Dissertation on

EARLY DETECTION OF RENAL BLOOD FLOW IMPEDANCE BY COLOR DOPPLER IN CHRONIC LIVER DISEASE WITH NORMAL RENAL PARAMETERS

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MADRAS MEDICAL COLLEGE,

CHENNAI - 600 003.

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CERTIFICATE

This is to certify that the dissertation entitled **"EARLY DETECTION OF RENAL BLOOD FLOW IMPEDANCE BY COLOR DOPPLER IN CHRONIC LIVER DISEASE WITH NORMAL RENAL PARAMETERS'** is a bonafide work done by **Dr.V.Dhurgesananthini** at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D.,Degree in General Medicine (Branch 1) under my guidance and supervision during the academic year 2010.

Prof.A.RADHAKRISHNAN, M.D,
Professor of medicine
Institute of Internal Medicine,
Madras Medical College &
Govt. General Hospital,
Chennai - 3.

Prof.C.RAJENDIRAN, M.D.,
Director and Professor,
Institute of Internal Medicine,
Madras Medical College &
Govt. General Hospital,
Chennai - 3.

PROF.J.MOHANASUNDARAM . M.D,Ph.D
DEAN
Madras Medical College & Govt. General Hospital,
Chennai - 3

DECLARATION

I **Dr.V.Dhurgesananthini** solemnly declare that **"EARLY DETECTION OF RENAL BLOOD FLOW IMPEDANCE BY COLOR DOPPLER IN CHRONIC LIVER DISEASE WITH NORMAL RENAL PARAMETERS''** was done by me at Madras Medical College and Government General Hospital, Chennai during 2010 under the guidance and supervision of my unit chief **PROF**.A**.RADHAKRISHNAN,M.D.,** Professor of medicine.

This dissertation is submitted to the Tamil Nadu Dr.M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D.Degree in General Medicine(Branch 1).

Place: Chennai-3 **Dr.V.Dhurgesananthini**

Date:

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Chennai - 3

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CONTENTS

INTRODUCTION

INTRODUCTION

Chronic liver disease in the clinical context is a disease process of the liver that involves a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis. **Cirrhosis** is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules (lumps that occur as a result of a process in which damaged tissue is regenerated)[52][53] leading to loss of liver function. Cirrhosis is most commonly caused by alcoholism, hepatitis B and C, and fatty liver disease, but has many other possible causes. Some cases are idiopathic, i.e., of unknown cause. Ascites (fluid retention in the abdominal cavity) is the most common complication of cirrhosis, and is associated with a poor quality of life, increased risk of infection, and a poor long-term outcome. Other potentially life-threatening complications are hepatic encephalopathy (confusion and coma) and bleeding from esophageal varices. Cirrhosis is generally irreversible, and treatment usually focuses on preventing progression and complications. In advanced stages of cirrhosis the only option is a liver transplant.

The word "cirrhosis" derives from Greek word κίρῥος, meaning *tawny* (the orange- yellow colour of the diseased liver). While the

clinical entity was known before, it was René Laennec who gave it the name "cirrhosis" in his 1819 work in which he also describes the stethoscope.[56]

CAUSES FOR CIRRHOSIS

Cirrhosis has many possible causes; sometimes more than one cause is present in the same patient. In the Western World, chronic alcoholism and hepatitis C, While in India alcoholism and hepatitis B are the most common causes.

- *Alcoholic liver disease* (ALD). Alcoholic cirrhosis develops for between 10% and 20% of individuals who drink heavily for a decade or more.(54) Alcohol seems to injure the liver by blocking the normal metabolism of protein, fats, and carbohydrates. Patients may also have concurrent alcoholic hepatitis with fever, hepatomegaly, jaundice, and anorexia. AST and ALT are both elevated but less than 300 IU/L with a AST:ALT ratio > 2.0, a value rarely seen in other liver diseases. Liver biopsy may show hepatocyte necrosis, Mallory bodies, neutrophilic infiltration with perivenular inflammation.

- *Chronic hepatitis C*. Infection with the hepatitis C virus causes inflammation of the liver and a variable grade of damage to the organ that over several decades can lead to cirrhosis. Cirrhosis caused by hepatitis C is the most common reason for liver transplant. Can be diagnosed with serologic assays that detect hepatitis C antibody or viral RNA. The enzyme immunoassay, EIA-2, is the most commonly used screening test in the US.

- *Chronic hepatitis B*. The hepatitis B virus causes liver inflammation and injury that over several decades can lead to cirrhosis. Hepatitis D is dependent on the presence of hepatitis B and accelerates cirrhosis in co-infection. Chronic hepatitis B can be diagnosed with detection of HBsAg over 6 months after initial infection. HBeAg and HBV DNA are determined to assess whether patient will need antiviral therapy.

- *Non-alcoholic steatohepatitis* (NASH). In NASH, fat builds up in the liver and eventually causes scar tissue. This type of hepatitis appears to be associated with diabetes, protein malnutrition, obesity, coronary artery disease, and treatment with corticosteroid medications. This disorder is similar to that of

alcoholic liver disease but patient does not have an alcohol history. Biopsy is needed for diagnosis.

- *Primary biliary cirrhosis*. Pt may be asymptomatic or may complain of fatigue, pruritus, and skin hyperpigmentation with hepatomegaly. There is prominent alkaline phosphatase elevation as well as elevations in cholesterol and bilirubin. Gold standard diagnosis is antimitochondrial antibodies with liver biopsy as confirmation if showing florid bile duct lesions. It is more common in women.

- *Primary sclerosing cholangitis*. PSC is a progressive cholestatic disorder presenting with pruritus, steatorrhea, fat soluble vitamin deficiencies, and metabolic bone disease. There is a strong association with inflammatory bowel disease (IBD), especially ulcerative colitis. Diagnosis is best with contrast cholangiography showing diffuse, multifocal strictures and focal dilatation of bile ducts, leading to a beaded appearance. Non-specific serum immunoglobulins may also be elevated.

- *Autoimmune hepatitis*. This disease is caused by the immunologic damage to the liver causing inflammation and

eventually scarring and cirrhosis. Findings include elevations in serum globulins, especially gamma globulins. Therapy with prednisone and/or azathioprine is beneficial. Cirrhosis due to autoimmune hepatitis still has 10-year survival of 90%+. There is no specific tool to diagnose autoimmune hepatitis but it can be beneficial to initiate a trial of corticosteroids.

- *Hereditary hemochromatosis*. Usually presents with family history of cirrhosis, skin hyperpigmentation, diabetes mellitus, pseudogout, and/or cardiomyopathy, all due to signs of iron overload. Labsoratory investigations will show fasting transferrin saturation of > 60% and ferritin > 300 ng/mL. Genetic testing may be used to identify *HFE* mutations. If these are present, biopsy may not need to be performed. Treatment is with phlebotomy to lower total body iron levels.

- *Wilson's disease*. Autosomal recessive disorder characterized by low serum ceruloplasmin and increased hepatic copper content on liver biopsy. Patient may also have Kayser-Fleischer rings in the cornea and altered mental status.

- *Alpha 1-antitrypsin deficiency* (AAT). Autosomal recessive disorder. Patients may also have emphysema , especially if they have a history of tobacco smoking. Serum AAT levels are low. Recombinant AAT is used to prevent lung disease due to AAT deficiency.

- *Cardiac cirrhosis*. Due to chronic right sided heart failure which leads to liver congestion.

- Galactosemia
- Glycogen storage disease type IV
- Cystic fibrosis
- Hepatotoxic drugs or toxins
- Certain parasitic infections (such as schistosomiasis)

GRADING

The severity of cirrhosis is commonly classified with the Child-Pugh score. This score uses bilirubin, albumin, INR, presence and severity of ascites and encephalopathy to classify patients in class A, B or C; class A has favourable prognosis, while class C is at high risk of death. It was devised in 1964 by Child and Turcotte and modified in 1973 by Pugh *et al.*.[55]

More modern scores, used in the allocation of liver transplants but also in other contexts, are the Model for End-Stage Liver Disease (MELD) score and its pediatric counterpart, the Pediatric End-Stage Liver Disease (PELD) score. The hepatic venous pressure gradient, i.e., the difference in venous pressure between afferent and efferent blood to the liver, also determines severity of cirrhosis, although hard to measure. A value of 16 mm or more means a great increased risk of dying.[57]

COMPLICATIONS

As the disease progresses, complications may develop. In some people, these may be the first signs of the disease.

- Bruising and bleeding resulting from decreased production of coagulation factors.
- Jaundice as a result of decreased processing of bilirubin.
- Itching (pruritus) because of bile salts products deposited in the skin.
- Hepatic encephalopathy - the liver does not clear ammonia and related nitrogenous substances from the blood, which are carried to the brain, affecting cerebral functioning: feeling to neglect of

personal appearance, unresponsiveness, forgetfulness, trouble concentrating, or changes in sleep habits.

- Sensitivity to medication caused by decreased metabolism of the active compounds.
- Hepatocellular carcinoma is primary liver cancer, a frequent complication of cirrhosis. It has a high mortality rate.
- Portal hypertension - blood normally carried from the intestines and spleen through the hepatic portal vein flows more slowly and the pressure increases; this leads to the following complications:
    - Ascites - fluid leaks through the vasculature into the abdominal cavity.
    - Esophageal varices - collateral portal blood flow through vessels in the stomach and esophagus. These blood vessels may become enlarged and are more likely to burst.
- Problems in other organs.
    - Cirrhosis can cause immune system dysfunction, leading to infection. Signs and symptoms of infection may be aspecific are more difficult to recognize (e.g., worsening encephalopathy but no fever).

- Fluid in the abdomen (ascites) may become infected with bacteria normally present in the intestines ie., SBP (spontaneous bacterial peritonitis).
- **Hepatorenal syndrome - insufficient blood supply to the kidneys, causing acute renal failure. This complication has a very high mortality (over 50%).**
- Hepatopulmonary syndrome - blood bypassing the normal lung circulation (shunting), leading to cyanosis and dyspnea (shortness of breath), characteristically worse on sitting up.[1]
- Portopulmonary hypertension - increased blood pressure over the lungs as a consequence of portal hypertension.[1]
- Portal hypertensive gastropathy which refers to changes in the mucosa of the stomach in patients with portal hypertension, and is associated with cirrhosis severity.

Hepatorenal syndrome (HRS) is the development of renal failure in patients with advanced chronic liver disease, occasionally fulminant hepatitis, who have portal hypertension and ascites. Estimates indicate

that at least 40% of patients with cirrhosis and ascites will develop HRS during the natural history of their disease.

During the 19th century, Frerichs and Flint [31] made the original description of renal function disturbances in liver disease. They described oliguria in patients with chronic liver disease in the absence of proteinuria and linked the abnormalities in renal function to disturbances present in the systemic circulation. In the 1950s, the clinical description of HRS by Sherlock, Popper, and Vessin[18] emphasized the functional nature of the syndrome, the coexistence of systemic circulatory abnormalities, and its dismal prognosis. Further studies in the following two decades demonstrated that renal failure occurred because of vasoconstriction of the renal circulation and intense systemic arteriolar vasodilatation resulting in reduced systemic vascular resistance and hypotension.

In HRS, the histological appearance of the kidneys is normal, and the kidneys often resume normal function following liver transplantation in most cases except 1-7% as mentioned later. This makes HRS a unique pathophysiological disorder that provides possibilities for studying the interplay between vasoconstrictor and vasodilator systems on the renal circulation.[2]

THERE ARE TWO WELL-DIFFERENTIATED CLINICAL PATTERNS OF HEPATO RENAL SYNDROME

TYPE 1 HEPATO RENAL SYNDROME

- Characterized by rapid and progressive impairment of renal function defined as a doubling of the initial serum creatinine to a level greater than 2.5 mg/dl or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 ml/min in less than 2 weeks.
- Usually occurs in severe liver failure (Jaundice, encephalopathy, and coagulopathy)
- Occurs frequently after certain precipitating factor (e.g. GI bleeding)
- Median survival time is only 2 weeks

TYPE 2 HEPATO RENAL SYNDROME

- Characterized by a less severe and non-progressive reduction of GFR.
- Associated with relatively preserved liver function.
- The main clinical consequence of this type of HRS is refractory ascites, due to a lack of response to diuretic.
- Median survival time is about 6 months.

CAUSES FOR HEPATORENAL SYNDROME

Risk factors for developing HRS have been reported based on a large series of patients with cirrhosis and ascites and, for the most part, are related to renal function.

Three important and easily recognized risk factors are

1. low mean arterial blood pressure (<80 mm Hg),
2. dilutional hyponatremia, and
3. severe urinary sodium retention (urine sodium <5 mEq/L).

Interestingly, patients with advanced liver disease, defined by a high Child-Pugh score or worsening parameters of liver function, such as low albumin, raised bilirubin, and increased prothrombin levels, are not at higher risk of developing HRS.

In some patients, HRS may occur spontaneously, whereas in others, it may be associated with infections (particularly SBP), acute alcoholic hepatitis, or large-volume paracentesis without albumin replacement. SBP precipitates type 1 HRS in approximately 20% of patients despite appropriate and timely diagnosis, treatment, and resolution of infection. Large-volume paracentesis without albumin replacement can precipitate type 1 HRS in up to 15% of patients.

The following is a list of risk factors associated with the development of HRS in patients with cirrhosis who are nonazotemic. All measurements were obtained after a minimum of 5 days on a low-salt diet and without diuretics.

- Low urinary sodium excretion (<5 mEq/L)
- Low serum sodium (dilutional hyponatremia)
- Reduced free-water excretion after water load
- Low mean arterial pressure
- High plasma renin activity
- Increased plasma norepinephrine
- Low plasma osmolality
- High urine osmolality
- High serum potassium
- Previous episodes of ascites
- Absence of hepatomegaly
- Presence of esophageal varices
- Poor nutritional status

PATHOGENESIS OF HEPATORENAL SYNDROME ARE

- Peripheral arterial vasodilation with hyperdynamic circulation and renal vasoconstriction[50].
- Stimulation of the renal sympathetic nervous system (SNS) and renal hypoperfusion.
- Cardiac dysfunction contributing to the circulatory derangements
- Action of different cytokines and vasoactive mediators on the renal circulation and other vascular beds.

FACTORS INVOLVED IN THE PATHOGENESIS OF HEPATO RENAL SYNDROME ARE;

- Disturbance in systemic hemodynamics (vasodilation mainly splanchnic).
- Increased activity of vasoconstrictor systems.
- Reduced activity of vasodilator systems.

VASODILATORS	**VASOCONSTRICTORS**
Prostaglandins	RAAS and Sympathetic(SNS)
Nitric oxide	ADH , Endothelin
Atrial natriuritic peptide	Adenosine, leukotrienes

FIGURE : 1

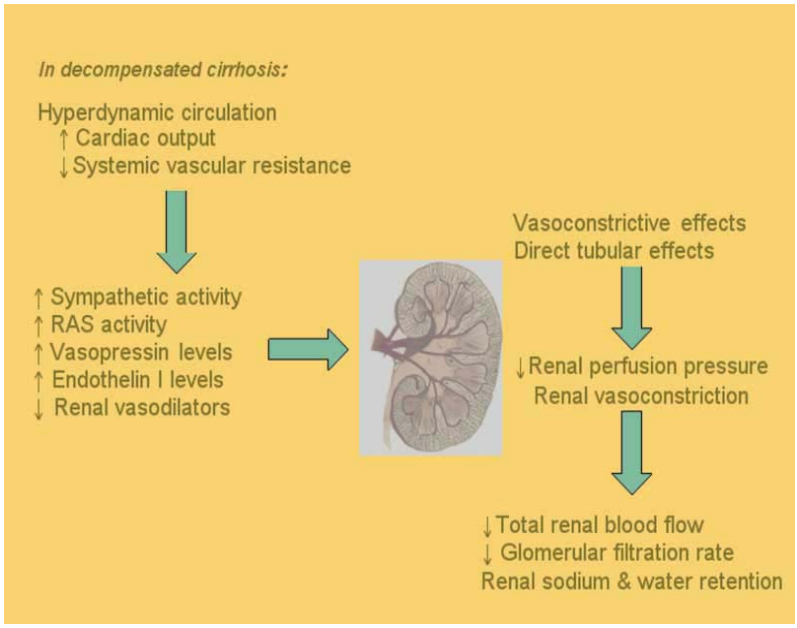
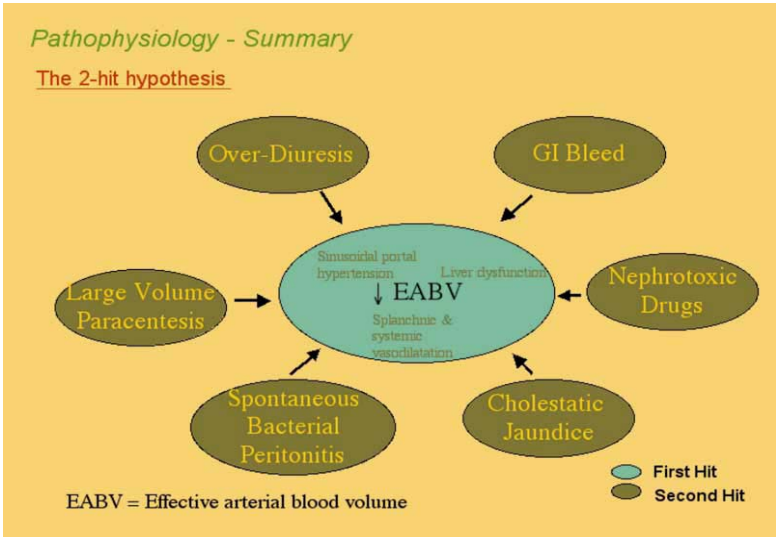


FIGURE : 2



The RAAS and SNS are the predominant systems responsible for renal vasoconstriction. The activity of both systems is increased in patients with cirrhosis and ascites, and this effect is magnified in HRS.

In contrast, an inverse relationship exists between the activity of these two systems and renal plasma flow (RPF) and the glomerular filtration rate (GFR)-(FIGURE-1) Endothelin is another renal vasoconstrictor present in increased concentration in HRS, although its role in the pathogenesis of this syndrome is yet to be identified.[12] Adenosine is well known for its vasodilator properties, although it acts as a vasoconstrictor in the lungs and kidneys. Elevated levels of adenosine are more common in patients with heightened activity of the RAAS and may work synergistically with angiotensin II to produce renal vasoconstriction in HRS. This effect has also been described with the powerful renal vasoconstrictor, leukotriene E4.

The vasoconstricting effect of these various systems is antagonized by local renal vasodilatory factors, the most important of which are the Prostaglandins. Perhaps the strongest evidence supporting their role in renal perfusion is the marked decrease in Renal Blood flow and the GFR when nonsteroidals, medications known to sharply reduce PG levels, are administered.

Nitric oxide (NO) is another vasodilator believed to play an important role in renal perfusion. Preliminary studies,predominantly from animal experiments, demonstrate that NO production is increased

in people with cirrhosis, although NO inhibition does not result in renal vasoconstriction due to a compensatory increase in PG synthesis. However, when both NO and PG production are inhibited, marked renal vasoconstriction develops.

These findings demonstrate that renal vasodilators play a critical role in maintaining renal perfusion, particularly in the presence of overactivity of renal vasoconstrictors. However, whether vasoconstrictor activity becomes the predominant system in HRS and whether reduction in activity of the vasodilatory system contributes to this have yet to be proven.

Various theories have been proposed to explain the development of HRS in cirrhosis. The two main theories are the arterial vasodilatation theory (FIGURE-1) and the hepatorenal reflex theory (FIGURE-3). The former theory not only describes sodium and water retention in cirrhosis, but also may be the most rational hypothesis for the development of HRS. Splanchnic arteriolar vasodilatation in patients with compensated cirrhosis and portal hypertension may be mediated by factors, the most important of which is probably NO. In the early phases of portal hypertension and compensated cirrhosis, this underfilling of the arterial bed causes a decrease in the effective arterial

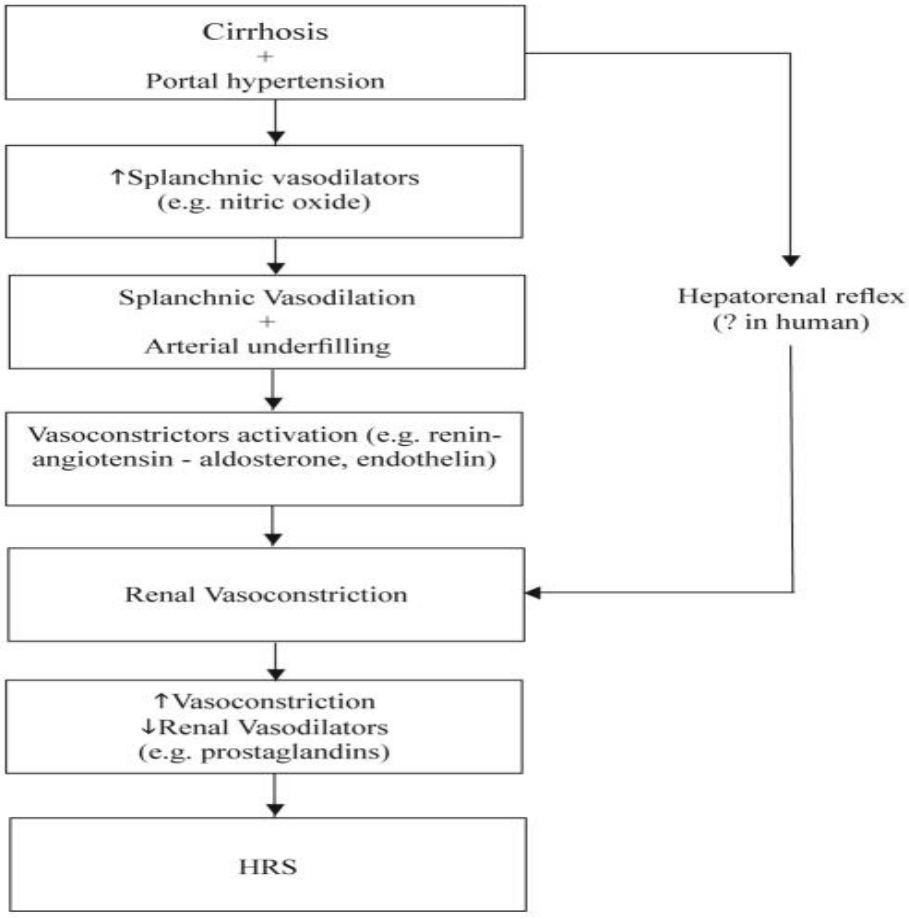
blood volume and results in homeostatic/reflex activation of the endogenous vasoconstrictor systems.

Activation of the RAAS and SNS occurs with antidiuretic hormone secretion, a later event when a more marked derangement in circulatory function is present. This results in vasoconstriction not only of the renal vessels, but also in vascular beds of the brain, muscle, spleen, and extremities. The splanchnic circulation is resistant to these effects because of the continuous production of local vasodilators such as NO.

In the early phases of portal hypertension, renal perfusion is maintained within normal or near-normal limits as the vasodilatory systems antagonize the renal effects of the vasoconstrictor systems. However, as liver disease progresses in severity, a critical level of vascular underfilling is achieved. Renal vasodilatory systems are unable to counteract the maximal activation of the endogenous vasoconstrictors and/or intrarenal vasoconstrictors, which leads to uncontrolled renal vasoconstriction. Support for this hypothesis is provided by studies in which the administration of splanchnic vasoconstrictors combination with volume expanders results in improvement in arterial pressure, RPF, and the GFR.The alternative

theory proposes that renal vasoconstriction in HRS is unrelated to systemic hemodynamics but is due to either in the synthesis of a vasodilatory factor or a hepatorenal reflex that leads to renal vasoconstriction. Evidence points to the vasodilation theory as a more tangible explanation for the development of HRS.

FIGURE : 3



THE INTERNATIONAL ASCITES CLUB HAS DEFINED CRITERIA FOR THE DIAGNOSIS OF HRS.

MAJOR AND MINOR CRITERIA, NECESSARY ONLY FOR THE DIAGNOSIS, ARE AS FOLLOWS:

MAJOR CRITERIA

- Chronic or acute liver disease with liver failure and portal hypertension
- Low glomerular filtration rate as indicated by a serum creatinine of 1.5mg/dL or a creatinine clearance of <40 mL/min
- Absence of shock, ongoing bacterial infection, and recent treatment with nephrotoxic drugs.
- Absence of excessive fluid loss including gastrointestinal loss
- No sustained improvement in renal function following expansion with 1.5 L of isotonic saline
- Proteinuria of <0.5 g/d and no ultrasonagraphic evidence of renal Disease

MINOR CRITERIA

- Urine volume < 500 mL/d
- Urine sodium >10 mmoL/d
- Urine osmolality >plasma osmolality
- Urine red cell count < 50 per high power field
- Serum sodium _<130 mmol/L

Of the various complications in liver cirrhosis including gastrointestinal bleeding, ascites and hepatocellular carcinoma, the rapidly progressive form of kidney dysfunction in cirrhosis, i.e. hepatorenal syndrome type 1, still carries the worst prognosis. In the early 1990s, median survival of these patients was reported to be as short as two weeks[20] and some more recent papers indicate that, in terms of prognosis, there has not been much progress since[6]. However, during the past two decades, new treatment concepts based on an improved pathophysiological understanding of the mechanisms ultimately leading to hepatorenal syndrome (HRS) have been introduced, and—very recently—a first randomized, controlled trial evaluating one of these concepts (i.e. vasoconstrictor treatment with the vasopressin analogue terlipressin) has been published in abstract form[48]. Despite successful drug treatment approaches, to date, the only

definitive treatment of HRS type 1 is liver transplantation or even combined liver/kidney transplantation in some patients.

The annual incidence of hepatorenal syndrome among adults with ascites and cirrhosis is approximately 8%. In addition, among adults with cirrhosis and portal hypertension, 20% develop hepatorenal syndrome in the first year after diagnosis, and as many as 40% of patients develop hepatorenal syndrome within 5 years after diagnosis.[1] Incidence data in children are scarce in literature; , their incidence of hepatorenal syndrome is essentially unknown at this time.

RACE

People of all races who have chronic liver disease are at risk for HRS.

SEX

Frequency is equal in both sexes.

AGE

Most patients with chronic liver disease are in their fourth to eighth decades of life.

MORTALITY/MORBIDITY

The median survival of adults with type 1 hepatorenal syndrome is estimated to be 2 weeks, and the hospital survival of the same patients is about 10%. In contrast, the median survival of individuals with type 2 hepatorenal syndrome is about 6 months. Survival and the recovery of renal function depend on the recovery of hepatic function, which is usually accomplished with liver transplantation in a minority of patients. About 1-7% of patients with hepatorenal syndrome develop end-stage renal disease and require dialysis despite liver transplantation and a recovery of hepatic function.

AIM AND OBJECTIVES

AIM AND OBJECTIVE

1. To assess the resistivity index of cirrhotics with ascites & cirrhotics without ascites.

2. To correlate with clinical status and s.creatinine levels.

3. To detect persons with Increased resistive index in the presence of normal renal parameters . And to identify a subset of patients at higher risk of development of HRS.

4. To find out the usefulness and applicability of this methodology.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY POPULATION

A total of 92 patients in which there were 75 cases which included cirrhosis with ascites, cirrhosis without ascites and 17 controls which included fatty liver and healthy individuals formed the study group.

Patients were selected for the study who satisfied all the inclusion and exclusion criteria. Written consent was obtained from all the patients participating in the study. All patients and controls were not from a single ethnic background.

STUDY DESIGN

Single centre, descriptive, cross sectional, non-interventional study.

INCLUSION CRITERIA

Patients attending Medical Gastroenterology clinic and General Medicine Wards with Chronic Liver Disease with or with out decompensation.

EXCLUSION CRITERIA

1. Preexisting renal parenchymal disease
2. Other causes of renal vasoconstriction
    - Drug-induced renal failure(e.g. aminoglycosides and NSAIDs)
    - Glomerulonephritis
    - Prerenal failure
    - Sepsis
    - Acute tubular necrosis

SAMPLE SIZE

92

MATERIALS AND METHODS

We prospectively studied 92 patients.

Detailed clinical history was taken from each patients and a complete review of their case notes performed. A complete clinical examination of the abdomen was done for each patient. Blood investigations were done. USG abdomen (FIGURE-4) was done which detects the liver echoes, ascitic fluid, kidney size .Portal Doppler was done to elicit portal hypertension picture. Renal Doppler (FIGURE-5) was done to measure the resistivity index, pulsatality index. The RI of three renal vessels, obtained in three renal areas, was measured in each

patient by using at least three Doppler spectra, and the mean value was calculated.

LABORATORY METHODS

In all the selected patients the following investigations were done;

LIVER FUNCTION TEST

RENAL FUNCTION TEST

SERUM SODIUM

USG ABDOMEN

PORTAL DOPPLER

RENAL DOPPLER

FIGURE : 4

USG ABDOMEN SHOWING BOTH THE KIDNEYS

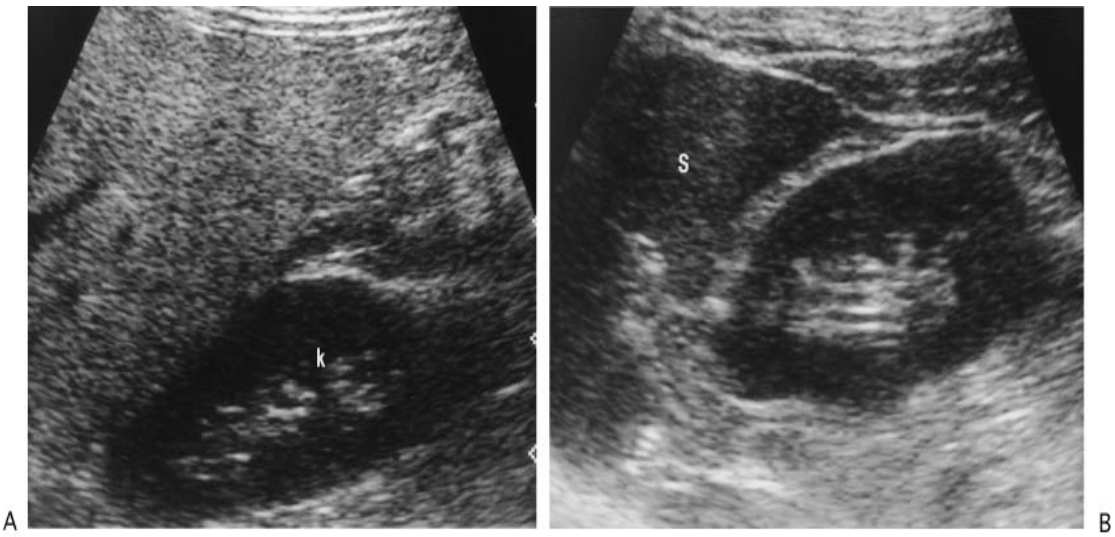
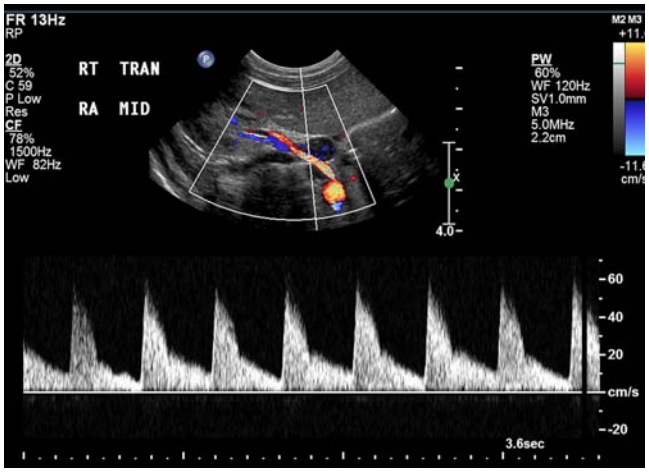


FIGURE : 5

RENAL DOPPLER SHOWING WAVE PATTERN



STATISTICAL ANALYSIS

The significance of difference between two proportions was indicated by the chi-square (x2) statistics. The significance of difference in mean between three groups was calculated by student t-test. Variables were considered to be significant if ($P<0.05$).

REVIEW OF LITERATURE

REVIEW OF LITERATURE

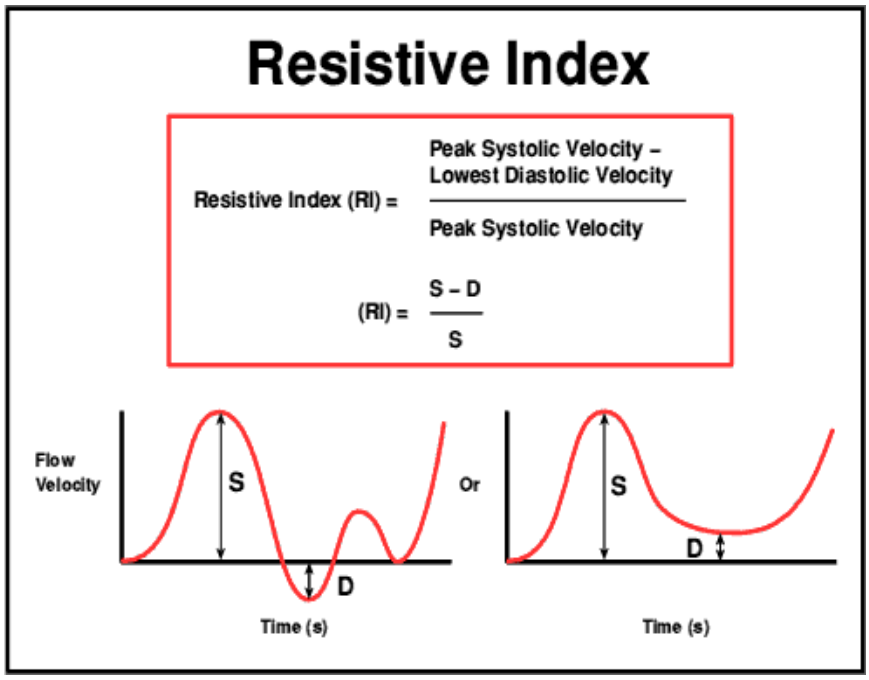
The association between liver disease and renal failure had been known for more than a hundred years. Frerichs, the founder of modern liver pathology, reported the presence of oliguria in patients with ascites in 1877[30]. Flint noted that in most cases of renal failure in cirrhosis, there were no significant histological changes in the kidneys at autopsy. In 1956, Hecker and Sherlock described renal failure in nine patients with liver disease characterised by progressive oliguria, very low urinary sodium excretion, hyponatraemia, but no proteinuria.[32] It was later established that the renal failure was functional, since the kidneys of these patients could be successfully transplanted to other patients with chronic renal failure, and the renal failure was reversible after liver transplantation.[33] Using clearance techniques, the hallmark of the HRS was found in 1967 to be severe renal vasoconstriction.[34]

The term "hepatorenal syndrome" was first used in 1939 to describe the occurrence of renal failure after biliary surgery or hepatic trauma. Later it was extended to other types of acute renal failure in liver diseases. In 1996, the International Ascites Club[2] proposed a new definition and diagnostic criteria for HRS, since then this term has been

generally accepted for the functional renalfailure that develops in patients with advanced cirrhosis.[11]

Renal Doppler ultrasonography

FIGURE :6



Hepatorenal syndrome (HRS) is characterized by renal vasoconstriction. Renal vasoconstriction has been documented in several series of cirrhotic patients by Doppler ultrasound (US) analysis of renal arteries, showing increased resistive index (RI) [(7)] which is determined from the spectral waveforms and corresponds to the following formula: (peak systolic frequency shift – lowest diastolic

frequency shift)/peak systolic frequency shift (FIGURE-6).**On average, renal RI is higher in cirrhotic patients compared to healthy individuals and high RI (over 0.7) can be observed in cirrhotic patients with serum creatinine within the normal range[7].** In patients without refractory ascites, RI decreases from the hilum towards the outer parenchyma, suggesting that the flow to the cortex is relatively preserved [7]. In contrast, in patients with refractory ascites, RI is also increased in the cortical vessels suggesting cortical vasoconstriction. Paracentesis and albumin infusion are followed by a significant decrease in renal RI [8]. Liver transplantation is also followed by a decrease in RI [10].

In patients with normal serum creatinine, increased RI seems to be correlated with a higher risk of subsequent deterioration in renal function[10] . Therefore, Doppler ultrasound may be an early marker of renal dysfunction. In candidates for transplantation, high renal RI is associated with a greater risk of renal dysfunction and dialysis post-transplantation.

Overall, Doppler US may be useful for identifying patients at high risk for developing impaired renal function at an early stage. It may be useful for clarifying the mechanisms involved in renal

insufficiency. It may help to clarify the role of therapeutic intervention on renal hemodynamics.

The intraparenchymal renal arterial RI was determined according Platt et al[19] and was as follows: RI equals (peak systolic frequency shift minus minimum diastolic frequency shift) divided by peak systolic frequency shift. The Doppler signal was recorded from both kidneys, from arcuate arteries of the corticomedullary junction, or from interlobar arteries along the margin of the medullary pyramids. To minimize sampling error, the Doppler spectrum was increased by using the lowest frequency-shift range possible without aliasing and a low-frequency (100-MHz) wall filter. **The RI of three renal vessels, obtained in three renal areas, was measured in each patient by using at least three Doppler spectra, and the mean value was calculated. A renal RI of 0.70 or more was considered abnormal and consistent with the presence of high renal vascular resistance and renal vasoconstriction [19]**

Early detection of renal vasoconstriction by Doppler predicts future development of HRS in patients with cirrhosis. In a prospective study done by Platt et al[19]. Patients with cirrhosis and elevated renal resistive indices and normal renal function have a 55% probability for

developing subsequent kidney dysfunction compared with 6% with normal indices. HRS develops in 26% of patients with elevated resistive indices compared with 1% of those with normal indices ($P < 0.001$).

In cirrhotic patients without ascites, standard kidney function tests and glomerular filtration rate (GFR) are normal . In non azotemic ascitic patients, GFR is normal or slightly reduced . Invasive methods have demonstrated that intrarenal blood flow is already reduced in the non ascitic phase of the disease and progressively decreases with disease evolution . Impaired renal perfusion plays a key role in sodium and fluid retention and severe renal vasoconstriction leads to the development of hepatorenal syndrome .

HEMODYNAMIC FINDINGS IN HEPATORENAL SYNDROME

Increased cardiac output

Reduced arterial pressure

Reduced total systemic vascular resistance

Increased total blood volume

Increased activity of vasoconstrictor systems

Increased portal pressure

Portosystemic shunting

Reduced splanchnic vascular resistance

Increased renal vascular resistance

Increased brachial and femoral artery resistance

Increased cerebral vascular resistance

Duplex evaluation of resistance indices represents a non-invasive method for estimating vascular resistance in the arterial bed downstream from the vessel in which they are calculated. Experimental studies have clearly demonstrated that in the kidney a linear correlation exists between resistance indices and decreasing organ perfusion caused by progressive gel microsphere embolization **An interesting finding in the current study is the increased renal vascular resistance in cirrhotic with normal kidney function**. **The increase in resistance indices is present in the non-ascitic phase of the disease and becomes more manifest after the development of ascites. The significant negative correlation between creatinine clearance and Pulsatality Index(PI) points to the role of renal vasoconstriction in the development of cirrhotic kidney disease.** However, PI is more accurate in differentiating abnormal waveforms because it takes into account the mean velocity. Sacerdoti et al[14] demonstrated a weak negative correlation between PI and RI and creatinine clearance in cirrhotic adult patients with normal kidney function. Derangement of renal perfusion in patients is related to the severity of liver disease as

evaluated with Child score. Resistance indices are higher among class C patients than class A and B. **There is also a significant positive relationship between resistance indices and the Child score**. Moreover, multiple regression analysis reveals that the severity of liver disease is the factor most affecting the levels of PI. Although it is known that kidney dysfunction is related to liver derangement, no evidence exists of a direct relationship between liver and kidney function.

In experimental models of cirrhosis, portal hypertension correlates with the reduction in GFR. The degree of portal hypertension was evaluated in our patients by duplex Doppler parameters and a matrix factor was extracted by regression analysis.

Renal vasoconstriction evaluated by these indices is correlated with Child score which quantitatively measures the hepatic function in cirrhosis.

Hence monitoring renal resistance indices, is an easy non-invasive method for studying the very early renal hemodynamic alterations in cirrhosis.

TWO SIMILAR STUDIES WERE SHOWN HERE

STUDY : 1

INTRA RENAL RESISTANCE INDEX FOR THE ASSESSMENT OF EARLY RENAL FUNCTION IMPAIRMENT IN PATIENTS WITH LIVER CIRRHOSIS. EUR J MED RES 2008 AUG 18;13(8);383-7

Renovascular vasoconstriction in patients with hepatorenal syndrome can be quantified by the renal arterial resistance index (RI). The study group investigated the value of RI measurement in detection of renal function impairment in patients with different stages of chronic liver disease.

Subjects were divided into 4 groups containing 21 patients with liver cirrhosis and ascites, 25 patients with liver cirrhosis without ascites, 35 patients with fatty liver disease and 78 control subjects. All patients underwent abdominal ultrasound examination with renal RI measurement and correlation with laboratory results for renal function.

It was found that RI was significantly higher in ascitic patients compared to non-ascitic patients (0.74 vs. 0.67, $p<0.01$) and in non-ascitic patients with liver cirrhosis than in control subjects (0.67 vs. 0.62, $p<0.01$). 48% (19/40) of patients with liver cirrhosis and normal serum creatinine concentration showed elevated RI levels. There were no significant differences in RI levels between patients with fatty liver disease and controls (0.63 vs. 0.62). Intrarenal RI measurement is a predictor of renal vasoconstriction and serves to detect early renal function impairment in cirrhotic patients. The diagnosis of elevated RI may be taken into account in the clinical management of these patients.

STUDY : 2

RENAL BLOOD FLOW DETECTION WITH DOPPLER ULTRASONOGRAPHY IN PATIENTS WITH HEPATIC CIRRHOSIS

Harika Çelebi, MD; Emir Dönder, MD; Hüseyin Çeliker, MD *Arch Intern Med.* 1997;157(5):564-566.

Hepatorenal syndrome, a well-recognized complication of established liver disease, is characterized by early renal vasoconstriction before clinically recognized renal disease. Renal vasoconstriction causes

increased renal vascular resistance, which can be detected noninvasively by Doppler ultrasonography.

OBJECTIVE

To detect early renal hemodynamic changes in patients with hepatic cirrhosis who had clinically normal renal functions. In the study there were Twenty patients with hepatic cirrhosis and ascites, 11 patients with hepatic cirrhosis without ascites, and 23 healthy control subjects. In was found that all cirrhotic patients had normal serum urea nitrogen and creatinine values. Peak systolic, peak diastolic, and mean flow velocities; pulsatile index; resistive index; and peak systolic velocity/peak diastolic velocity ratio as measured by renal Doppler ultrasonography. It was found that Peak diastolic flow velocity was significantly lower in cirrhotic patients with ascites than in cirrhotic patients without ascites and control subjects ($P<.02$ and $P<.004$, respectively), but the peak systolic flow velocity/peak diastolic flow velocity ratio ($P<.007$ and $P<.001$, respectively), pulsatile index ($P<.007$ and $P<.001$, respectively), and resistive index ($P<.007$ and $P<.001$, respectively) were significantly higher in cirrhotic patients with ascites than in cirrhotic patients without ascites and controls. This lead the research group to conclude that Renal Doppler ultrasonography can

noninvasively identify a subgroup of nonazotemic patients with hepatic cirrhosis who are at high risk for subsequent development of renal dysfunction and hepatorenal syndrome. Arch Intern Med.1997;157:564-566

GENERAL RECOMMENDATIONS FOR THE RATIONAL MEDICAL THERAPY OF ASCITES IN PATIENTS WITH CIRRHOSIS

1. Patients who develop moderate ascites for the first time should receive an aldosterone antagonist such as spironolactone alone, starting from 100 mg/day increasing to maximum of 400 mg/day (level 1). In patients who do not respond to aldosterone antagonists, as defined by a reduction of body weight of less than 2 kg/wk, or in patients who develop hyperkalemia, furosemide should be added at an increasing dose from 40 mg/day to a maximum of 160 mg/day(level 1). Patients should undergo regular clinical and biochemical monitoring during the first month of treatment.

2. Patients who develop recurrent moderate ascites should be treated with a combination of an aldosterone antagonist plus furosemide, whose dose should be increased sequentially as above.

3. The maximum recommended weight loss during diuretic therapy should be, 0.5 kg/day in patients without edema,and 1 kg/day in patients with significant edema.

4. The goal of long-term treatment is to keep patients free of ascites with the minimum dose of diuretics. Therefore, once the ascites has been largely resolved the dose of diuretics should be reduced or discontinued if possible.

5. Patients who are not responsive to top diuretic doses or those who develop serious complications under diuretic treatment should be checked for refractory ascites. First of all, the compliance with low-sodium diet should be checked by determining urine sodium excretion in these patients.

6. Since therapeutic paracentesis results in a more rapid resolution of ascites with a lower incidence of complications compared with diuretic treatment, paracentesis is the first-line therapy in patients with tense ascites.

7. Therapeutic paracentesis is also the first-line treatment in patients with refractory ascites.

8. Therapeutic paracentesis should be completed in a single session.

9. Since the removal of a large amount of ascitic fluid can cause impairment of circulatory function leading to renal failure and/or hyponatremia, it is necessary to prevent these circulatory changes. The best method to prevent circulatory dysfunction is the administration of albumin at a dose of 8 g/L of ascitic fluid removed.

10. In patients undergoing therapeutic paracentesis of half L of ascites, the use of alternative plasma expanders is not recommended since they are less effective in preventing postparacentesis circulatory dysfunction.

11. After therapeutic paracentesis, patients should receive the minimum dose of diuretics necessary to prevent the reaccumulation of ascites

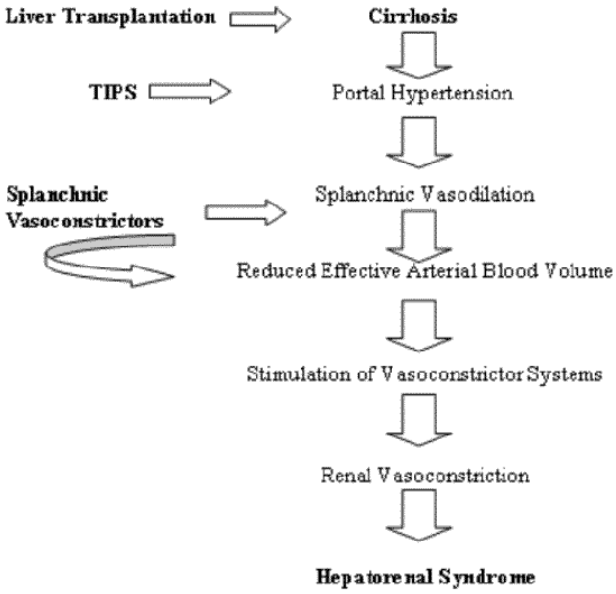
Prevention

The risk of death in hepatorenal syndrome is very high; consequently, there is a significant emphasis on the identification of patients who are at risk for HRS, and prevention of triggers for onset of HRS. As infection (specifically spontaneous bacterial peritonitis) and gastrointestinal hemorrhage are both complications in individuals with cirrhosis, and are common triggers for HRS, specific care is made in early identification and treatment of cirrhotics with these complications to prevent HRS.[5] Some of the triggers for HRS are induced by treatment of ascites and can be preventable. The aggressive use of diuretic medications should be avoided. In addition, many medications that are either used to treat cirrhotic complications (such as some antibiotics) or other conditions may cause sufficient impairment in renal function in the cirrhotic to lead to HRS.[4][5] Also, large volume paracentesis—which is the removal of ascites fluid from the abdomen using a needle or catheter in order to relieve discomfort—may cause enough alteration in hemodynamics to precipitate HRS, and should be avoided in individuals at risk. The concomitant infusion of albumin can avert the circulatory dysfunction that occurs after large volume paracentesis, and may prevent HRS.[5] Conversely, in individuals with

very tense ascites, it has been hypothesized that removal of ascitic fluid may improve renal function if it decreases the pressure on the renal veins.[5]

FIGURE : 7

Attempts at reversing HRS have required intervening on the individual steps



PITFALLS

- Nephrotoxic agents should be avoided because of the risk of developing HRS. Drugs that are commonly associated with HRS in patients with cirrhosis are nonsteroidals, aspirin, aminoglycosides, and iodine-containing contrast agents.

- A diagnostic paracentesis should be considered in all patients who have cirrhosis with ascites who develop HRS, to exclude the presence of SBP. Few, if any, contraindications exist for a diagnostic paracentesis, and the use of empiric antibiotics in this situation is not justified.

- Other causes of renal failure need to be considered in the differential diagnosis, and assuming that all patients who have cirrhosis with renal impairment have HRS is wrong. A standardized approach to the evaluation of renal failure not only confirms HRS, it also identifies conditions that may be reversible.

- In patients with cirrhosis who have decompensated, evaluation of candidacy for liver transplantation should be performed before the onset of HRS. This helps physicians decide/stratify the aggressiveness of treatment when HRS develops. Liver transplant evaluation in a hospitalized patient with type 1 HRS may be too late, given the dearth of donors.

RESULTS AND OBSERVATION

RESULTS AND OBSERVATION:

AGEWISE CLASSIFICATION;

FIGURE : 8

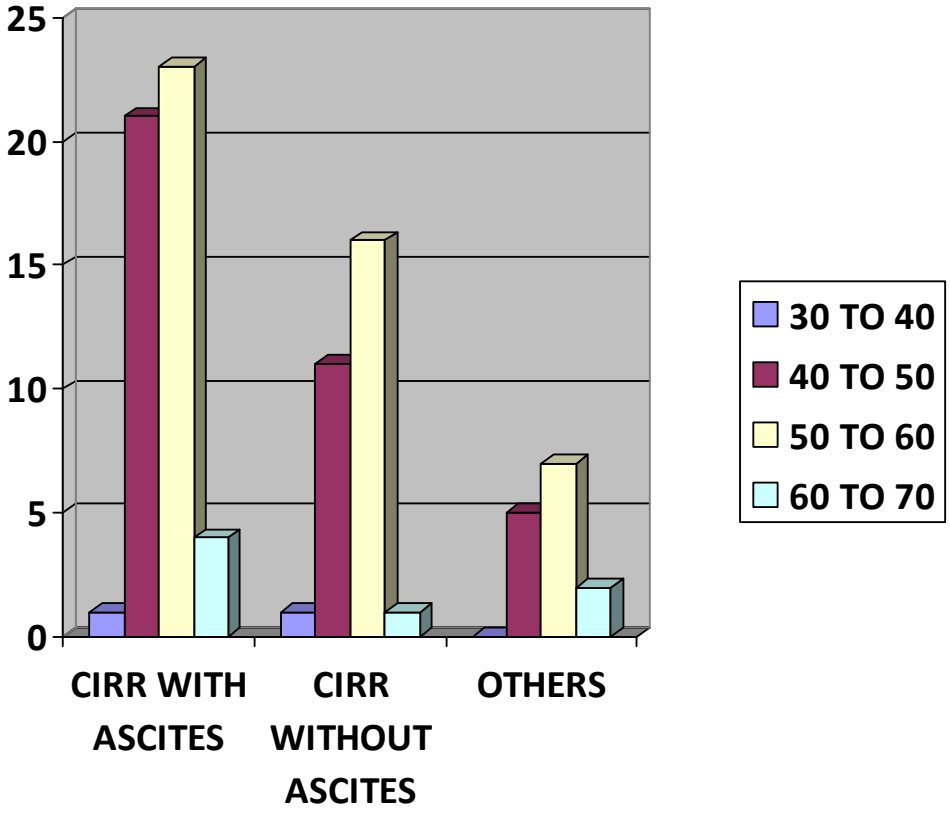


TABLE : 1

AGE IN YRS	CIRRHOSIS WITH ASCITES	CIRRHOSIS WITHOUT ASCITES	HEALTHY
30-40	**01(1%)**	**01(1%)**	**0**
40-50	**21(23%)**	**10(12%)**	**06(05%)**
50-60	**23(25%)**	**14(18%)**	**09(08%)**
60-70	**04(4%)**	**01(1%)**	**02(2%)**

Among 92, 25% of cirrhosis with ascites patients falls in the age group of 50 to 60 years,23% are in the age group of 40 to 50 years.

Can J Gastroenterol. 2004 Feb;18(2):121-2.

Am J Gastroenterol. 2002 Aug;97(8):1868-70.

Above mentioned study shows mean age of 39 to 63 years. In our study mean age group falls between 33 to 64 years (figure-8).

SEXWISE CLASSIFICATION

FIGURE : 9

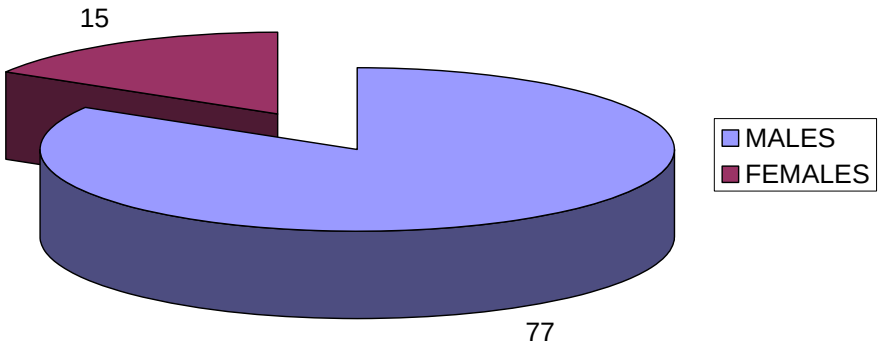


TABLE : 2

MALES	**77**	**84 %**
FEMALES	**15**	**16 %**

Can J Gastroenterol. 2004 Feb;18(2):121-2.

Am J Gastroenterol. 2002 Aug;97(8):1868-70.

Out of the total of 92 patients 77 were males,15 were females. In the above mentioned study 67% were males compared to our study (figure-9) which shows 84% males .

ALCOHOLIC VS NON ALCOHOLIC

FIGURE : 10

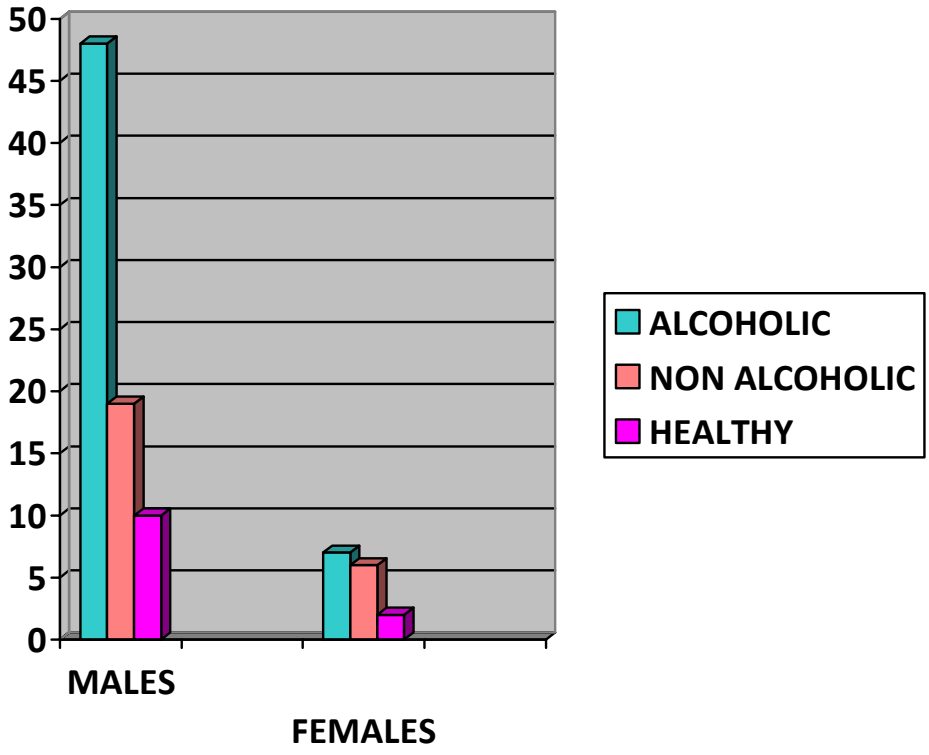


TABLE :3

	MALES	**FEMALES**
ALCOHOLIC	48(52%)	07(8%)
NON ALCOHOLIC	19(21%)	06(6%)
HEALTHY	10(11%)	02(2%)

Out of the 77 males 52%were alcoholic and 8% of females also were alcoholic.

CIRRHOSIS WITH ASCITES/NONASCITES

FIGURE : 11

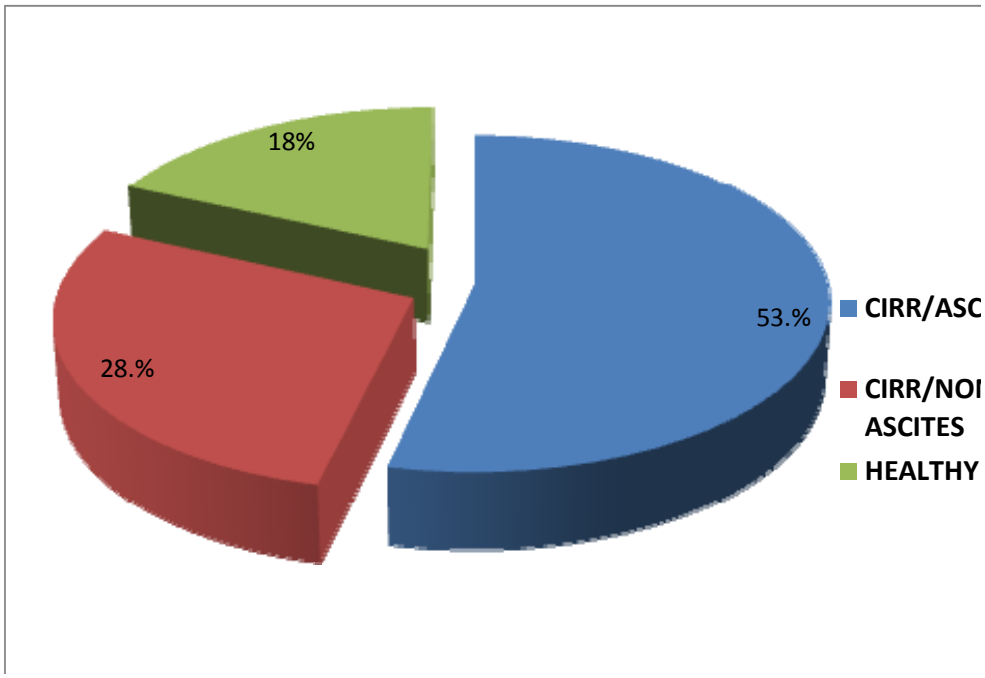


TABLE : 4

CIRRHOSIS/ASCITES	**49(53%)**
CIRRHOSIS/NON ASCITES	**26(28%)**
HEALTHY	**17(18%)**

Total 92 patients, 49 were cirrhosis with ascites patients, 26 were cirrhosis without ascites patients,17 healthy which includes fatty liver also.

CLASSIFICATION BASED ON CAUSES

FIGURE : 12

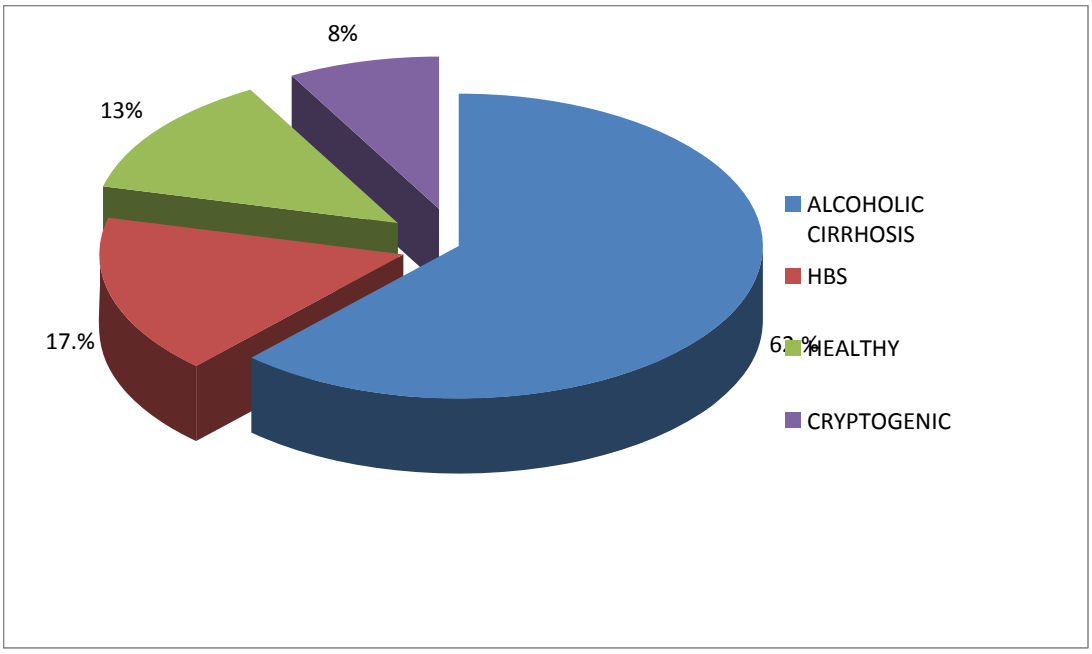


TABLE : 5

ALCOHOLIC CIRRHOSIS	**57**	**62%**
HBS	**16**	**17%**
CRYPTOGENIC	**7**	**8%**
HEALTHY	**12**	**13%**

Alcoholic cirrhosis is 62%,17% were hepatitis B positive and 8% were of cryptogenic cause.

RESISTIVITY INDEX IN VARIOUS GROUPS

FIGURE : 13

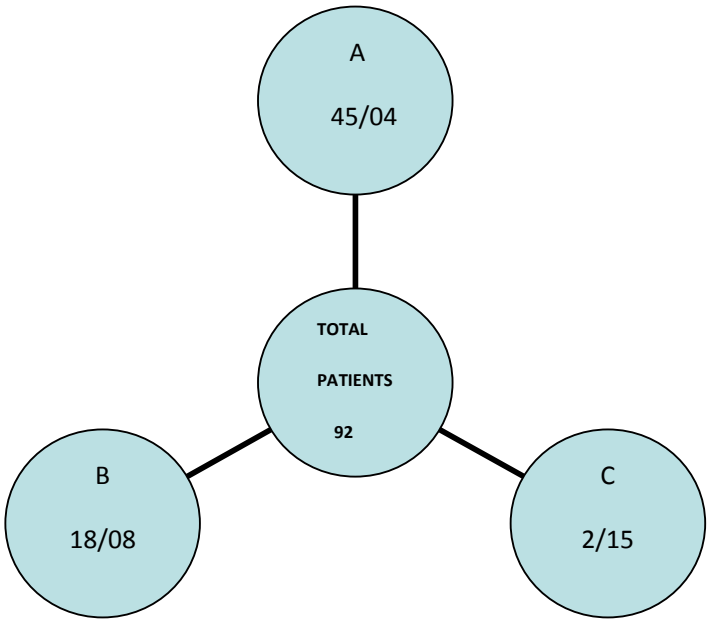
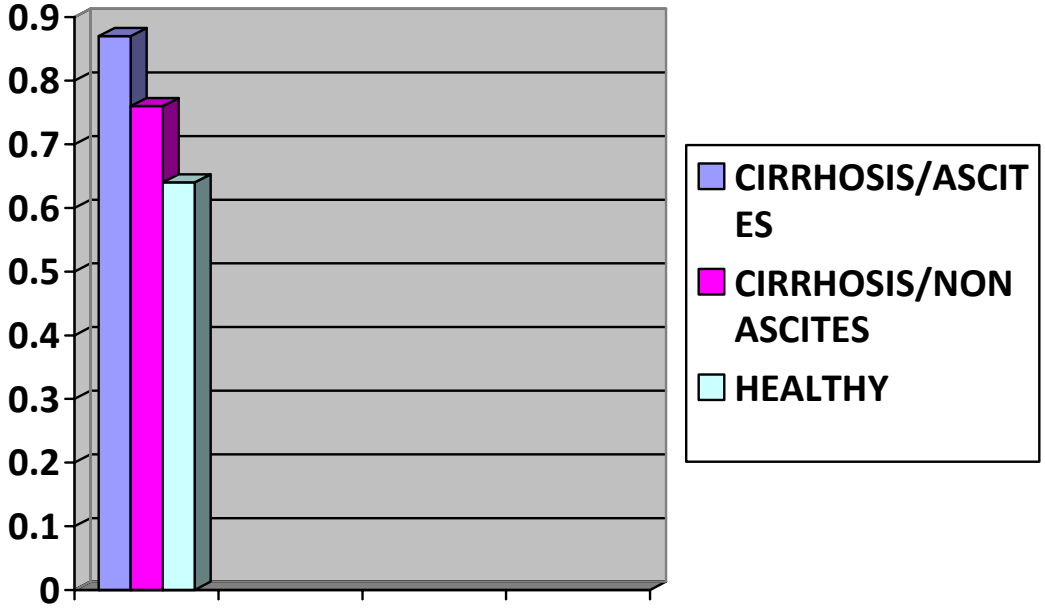


TABLE : 6

GROUPS	CATAGORIES	ELEVATED RI	NORMAL RI
A	**CIRRHOSIS/ASCITES**	**45**	**04**
B	**CIRRHOSIS/NON ASCITES**	**18**	**08**
C	**FATTY LIVER/HEALTHY**	**02**	**15**

COMPARING RESISTIVITY INDICES

FIGURE : 14



A renal RI of 0.70 or more was considered abnormal according to the study of Platt JF, Ellis JH, Rubin JM, Merion RM, Lucey MR: Renal duplex Doppler ultrasonography: A noninvasive predictor of kidney dysfunction hepatorenal failure in liver disease. Hepatology 20:362 –369,1994

TABLE : 7

	RI
CIRRHOSIS/ASCITES	**>0.87**
CIRRHOSIS/NON ASCITES	**>0.76**
HEALTHY	**>0.64**

In our study(figure-13) Resistivity index is increased in both cirrhosis with ascites and without ascites. So early phase itself shows increased RI. **In Eur J Med Res. 2008 Aug 18;13(8):383-7, RI was significantly higher in ascitic patients compared to non-ascitic patients (0.74 vs. 0.67, p<0.01) and in non-ascitic patients with liver cirrhosis than in control subjects (0.67 vs. 0.62, p<0.01).** In our study RI was significantly higher in ascitic patients compared to non-ascitic patients (0.87 vs. 0.76, p<0.01) and in non-ascitic patients with liver cirrhosis than in control subjects (0.76 vs. 0.64, p<0.001) .

PROBABILITY OF HRS IN CIRRHOSIS WITH ASCITES

FIGURE : 15

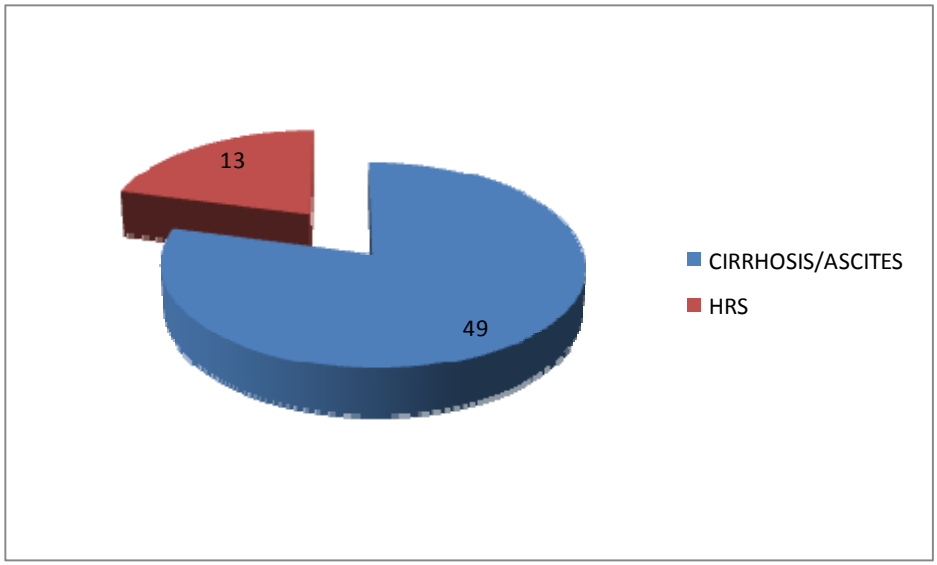


TABLE : 8

CIRRHOSIS WITH ASCITES	**49 patients**
PROBABILITY OF HEPATORENAL	**13 patients**

Considering various studies the probability of HRS in cirrhosis with ascites is 26% .

EXPECTED MORTALITY 1YR&5YR

FIGURE : 16

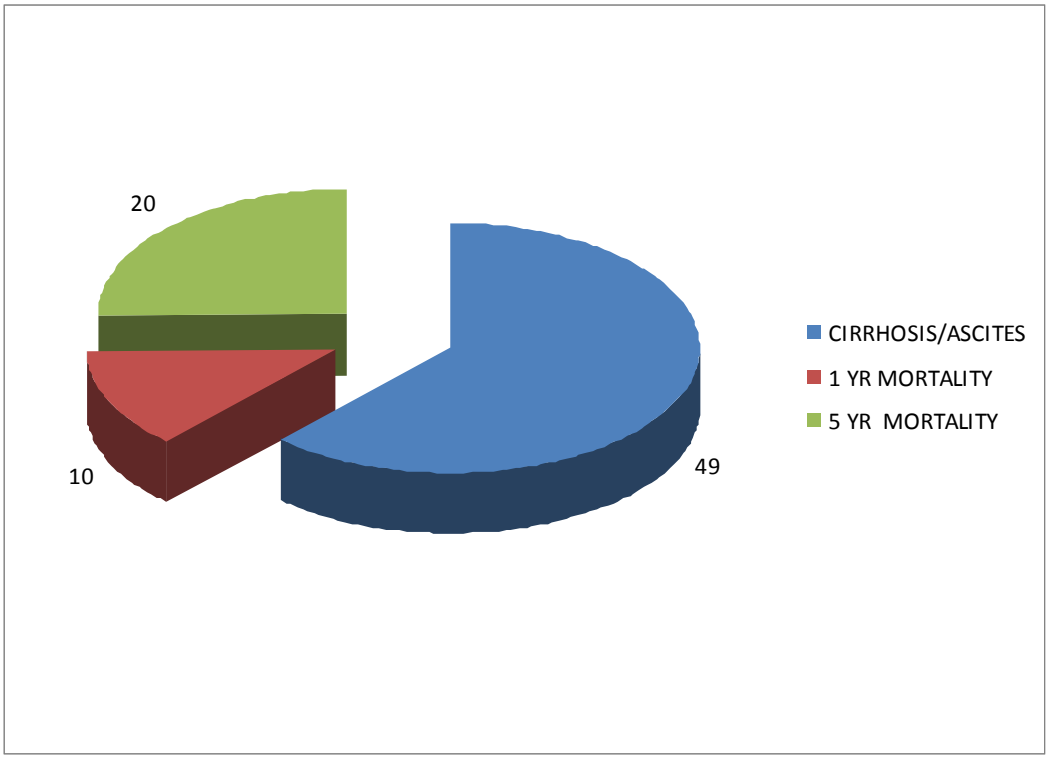


TABLE: 9

WITH ASCITES		**49**
1 YR MORTALITY	**20%**	**10**
5 YR MORTALITY	**40%**	**20**

PULSATALITY INDEX

FIGURE : 17

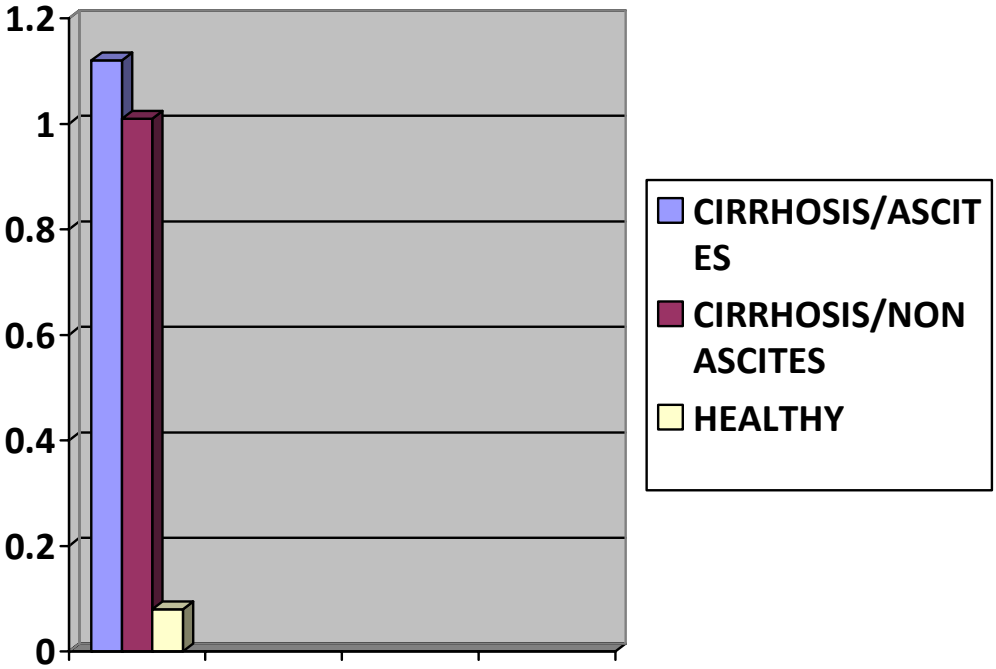


TABLE : 10

	PI
CIRRHOSIS/ASCITES	**>1.12**
CIRRHOSIS/NON ASCITES	**>1.01**
HEALTHY	**>0.08**

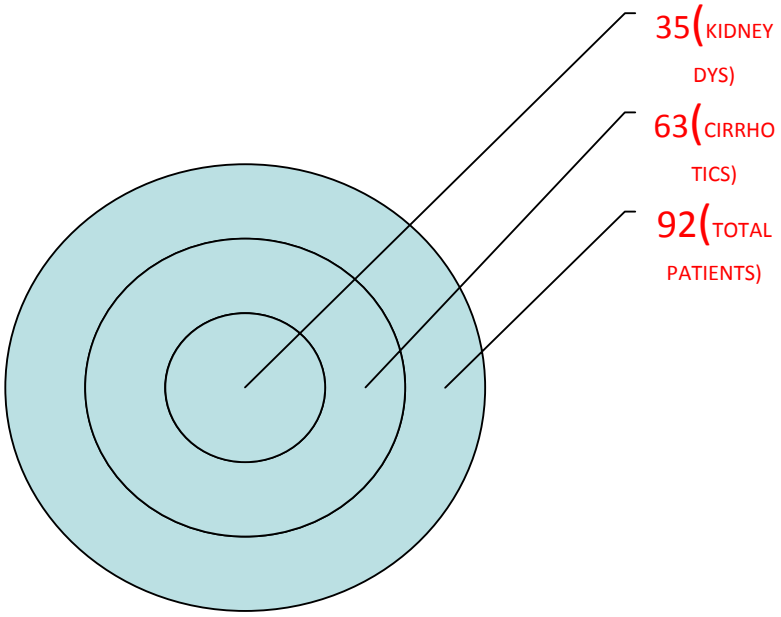
PI is increased in cirrhosis with ascites patients compared to cirrhotics without ascites (1.12 vs1.02), cirrhotics without ascites and healthy (1.02vs0.08).

55% CIRRHOSIS WITH ELEVATED RI AND NORMAL RENAL FUNCTION DEVELOPS SUBSEQUENT KIDNEY DYSFUNCTION

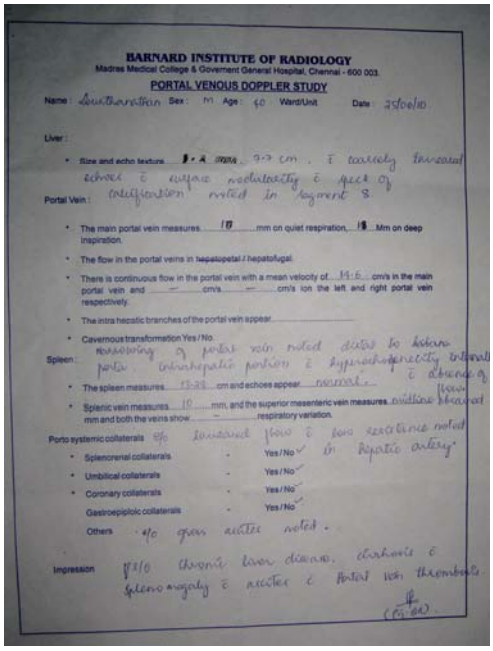
TABLE :11

TOTAL NO OF PATIENTS	**92 PATIENTS**	
CIRRHOTICS WITH ELEVATED RI	**63PATIENTS**	**35 PATIENTS**

FIGURE : 18



PORTAL DOPPLER RESULT



BARNARD INSTITUTE OF RADIOLOGY
Madras Medical College & Government General Hospital, Chennai - 600 003.

PORTAL VENOUS DOPPLER STUDY

Name: Sivatharshini Sex: F Age: 40 Ward/Unit Date: 25/06/10

Liver:

- Size and echo texture: [illegible] 9.7 cm. Is coarsely increased echoes & ill-defined nodularity & piece of calcification noted in segment 8.

Portal Vein:

- The main portal vein measures 10 mm on quiet respiration, 15 Mm on deep inspiration.
- The flow in the portal veins in hepatopetal / hepatofugal.
- There is continuous flow in the portal vein with a mean velocity of 14.6 cm/s in the main portal vein and — cm/s — cm/s ion the left and right portal vein respectively.
- The intra hepatic branches of the portal vein appear
- Cavernous transformation Yes / No

Spleen: Reversing of portal vein noted distal to hilum. Intrahepatic portion & hypertrophy & observed. Splenic artery flow & normal.

- The spleen measures 13.2 cm and echoes appear normal.
- Splenic vein measures 10 mm, and the superior mesenteric vein measures within normal mm and both the veins show — respiratory variation.

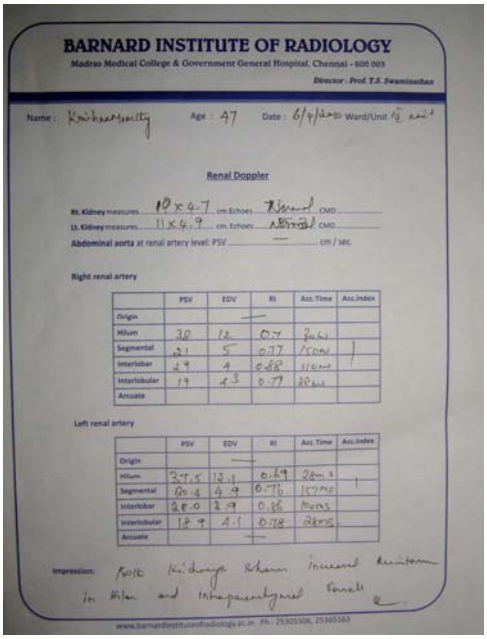
Porto systemic collaterals: o/o Increased flow & low resistance noted in hepatic artery.

- Splenorenal collaterals - Yes / No
- Umbilical collaterals - Yes / No
- Coronary collaterals - Yes / No
- Gastroepiploic collaterals - Yes / No

Others: o/o gross ascites noted.

Impression: F/o chronic liver disease, cirrhosis & splenomegaly & ascites & portal vein thrombosis (PVT).

RENAL DOPPLER RESULT



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Madras Medical College & Government General Hospital, Chennai - 600 003
Director : Prof. T.S. Swaminathan

Name: Kaliyamoorthy Age: 47 Date: 6/4/2010 Ward/Unit IP No.

Renal Doppler

Rt. Kidney measures 10 x 4.7 cm. Echoes Normal CMD
Lt. Kidney measures 11 x 4.9 cm. Echoes Normal CMD
Abdominal aorta at renal artery level: PSV — cm / sec.

Right renal artery

	PSV	EDV	RI	Acc.Time	Acc.Index
Origin			—		
Hilum	38	12	0.7	76ms	
Segmental	21	5	0.77	150ms	
Interlobar	29	4	0.88	110ms	
Interlobular	19	1.3	0.79	80ms	
Arcuate					

Left renal artery

	PSV	EDV	RI	Acc.Time	Acc.Index
Origin			—		
Hilum	37.5	12.4	0.69	86m.s	
Segmental	20.4	4.9	0.76	157ms	
Interlobar	28.0	2.9	0.86	80ms	
Interlobular	12.9	1.1	0.78	82ms	
Arcuate			—		

Impression: Both kidneys shows increased resistance in hilar and intraparenchymal vessels.

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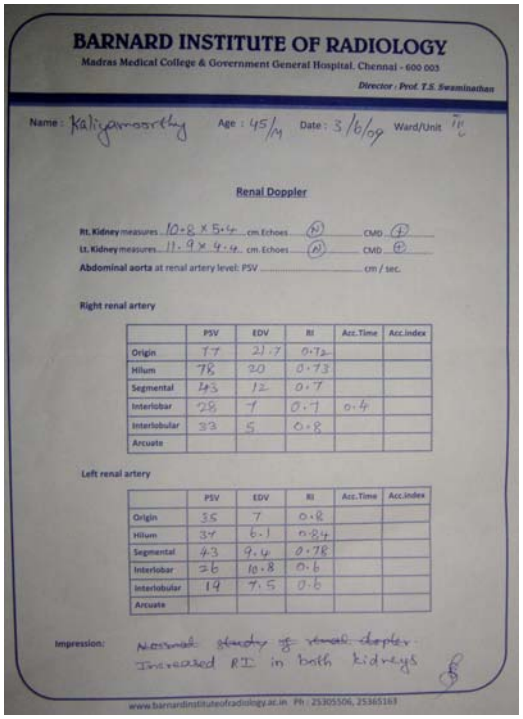
RENAL DOPPLER RESULT



BARNARD INSTITUTE OF RADIOLOGY
Madras Medical College & Government General Hospital, Chennai - 600 003
Director : Prof. T.S. Swaminathan

Name: Kaliyamoorthy Age: 45/M Date: 3/6/09 Ward/Unit IP

Renal Doppler

Rt. Kidney measures 10.8 x 5.4 cm. Echoes N CMD +
Lt. Kidney measures 11.9 x 4.4 cm. Echoes N CMD +
Abdominal aorta at renal artery level: PSV ..... cm / sec.

Right renal artery

	PSV	EDV	RI	Acc.Time	Acc.Index
Origin	77	21.7	0.72		
Hilum	78	20	0.73		
Segmental	45	12	0.7		
Interlobar	28	7	0.7	0.4	
Interlobular	33	5	0.8		
Arcuate					

Left renal artery

	PSV	EDV	RI	Acc.Time	Acc.Index
Origin	35	7	0.8		
Hilum	34	6.1	0.84		
Segmental	43	9.4	0.78		
Interlobar	26	10.8	0.6		
Interlobular	14	7.5	0.6		
Arcuate					

Impression: Normal ~~study of renal doppler~~. Increased RI in both kidneys

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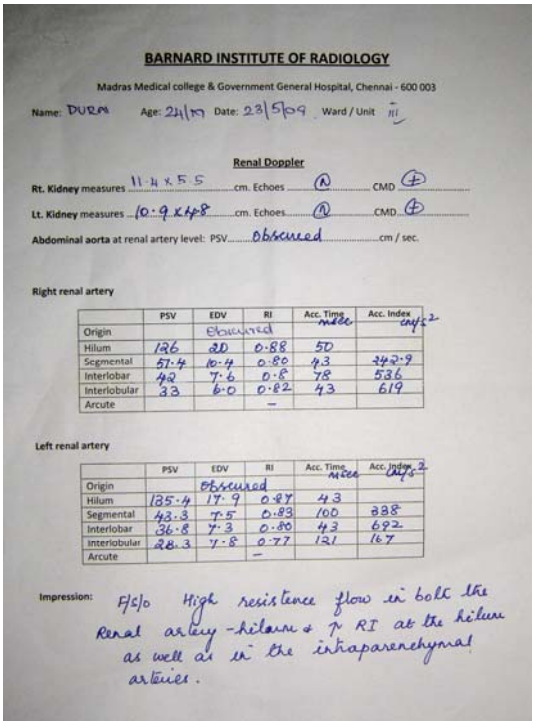
RENAL DOPPLER RESULT



BARNARD INSTITUTE OF RADIOLOGY
Madras Medical college & Government General Hospital, Chennai - 600 003

Name: DURA Age: 21/M Date: 23/5/09 Ward / Unit IP

Renal Doppler

Rt. Kidney measures 11.4 x 5.5 cm. Echoes N CMD +
Lt. Kidney measures 10.9 x 4.8 cm. Echoes N CMD +
Abdominal aorta at renal artery level: PSV Obscured cm / sec.

Right renal artery

	PSV	EDV	RI	Acc. Time	Acc. Index
Origin		Obscured		Acc	Graft 2
Hilum	126	20	0.88	50	
Segmental	57.4	10.4	0.80	43	242.9
Interlobar	42	7.6	0.8	78	536
Interlobular	33	6.0	0.82	43	619
Arcute			—		

Left renal artery

	PSV	EDV	RI	Acc. Time	Acc. Index
Origin		Obscured		Acc	Graft 2
Hilum	135.4	17.9	0.87	43	
Segmental	43.3	7.5	0.83	100	388
Interlobar	36.8	7.3	0.80	43	692
Interlobular	28.3	7.8	0.77	121	167
Arcute			—		

Impression: F/o High resistance flow in both the Renal artery - hilum & ↑ RI at the hilum as well as in the intraparenchymal arteries.

RESULTS

In my study, I found that

Elevated RI 65/92=71%

Normal RI 27/92=29%

GROUPS	CATAGORIES	ELEVATED RI	NORMAL RI
A	CIRRHOSIS/ASCITES	45	04
B	CIRRHOSIS/NON ASCITES	18	08
C	FATTY LIVER/HEALTHY	02	15

Comparing A and B groups that is cirrhosis with ascites (A),cirrhosis without ascites (B)

GROUPS	CATAGORIES	ELEVATED RI	NORMAL RI
A	CIRRHOSIS/ASCITES	45	4
B	CIRRHOSIS/NON ASCITES	18	8

GROUPS		ELEVATED RI	NORMAL RI
A	OBSERVED	45	4
	EXPECTED	41	8
B	OBSERVED	18	8
	EXPECTED	22	4

X^2 =E (observed-expected)^2 /expected+(observed- expected)^2 /expected

X^2 =E (45-41)^2/41+(4-8)^2/8+(18-22)^2/22+(8-4)^2/4

= 0.39+2+0.72+4

=7.11

P VALUE<.01

Comparing B group and C group that is cirrhosis without ascites (B), fatty liver/healthy(C).

GROUPS	CATAGORIES	ELEVATED RI	NORMAL RI
B	CIRRHOSIS WITHOUT ASCITES	18	8
C	FATTY LIVER HEALTHY	2	15

GROUPS		ELEVATED RI	NORMAL RI
B	OBSERVED	18	8
	EXPECTED	12	14
C	OBSERVED	2	15
	EXPECTED	8	9

X^2 =E (observed-expected)^2 /expected+(observed- expected)^2 /expected

X^2 =E(18-12)^2 /12 +(8-14)^2/14+(2-8)^2/8+(15-9^2)/9

X^2=3+2.5+4.5+4

=14

P VALUE <.001

In our study RI was significantly higher in ascitic patients compared to non-ascitic patients (0.87 vs. 0.76, $p<0.01$) and in non-ascitic patients with liver cirrhosis than in control subjects (0.76 vs. 0.64, $p<0.001$) .

DISCUSSION

DISCUSSION

As the majority of individuals with hepatorenal syndrome have cirrhosis, much of the epidemiological data on HRS comes from the cirrhotic population. The condition is quite common: approximately 10% of individuals admitted to hospital with ascites have HRS.[57] A retrospective case series of cirrhotic patients treated with terlipressin suggested that 20.0% of acute renal failure in cirrhotics was due to type 1 HRS, and 6.6% was due to type 2 HRS It is estimated that 18% of individuals with cirrhosis and ascites will develop HRS within one year of their diagnosis with cirrhosis, and 39% of these individuals will develop HRS within five years of diagnosis.[57]

The mean age was 51.8 +/- 12.1 yr, and 67% were male as per the study on Hepatorenal syndrome: diagnostic accuracy, clinical features, and outcome in a tertiary care center. Watt K, Uhanova J, Minuk GY. Liver Diseases Unit, University of Manitoba, Winnipeg, Canada.Comment in: Can J Gastroenterol. 2004 Feb;18(2):121-2. Am J Gastroenterol. 2002 Aug;97(8):1868-70.

In our study 92 patients were studied including cirrhosis with ascites(49),without ascites(26),fatty liver and healthy individuals(17).

Many of them are in the fourth (40%) and fifth (51%) decades. Males (84%) are more common than females (16%), whereas in the above study by university of Canada, percentage of females was higher. 60% were alcoholic and 25% were non alcoholic. Of the various causes apart from alcoholic , 17% were hepatitis B positive, 8% were cryptogenic,13% were healthy.

According to the study by Recommendations available for managing ascites, SBP and hepatorenal syndrome 3. August 2010 05:53 "It is estimated that almost 60 percent of cirrhotic patients develop ascites within 10 years of their disease, which is a huge proportion of patient .In our study 49 (53%) were cirrhosis with ascites patients, 26 (28%) were cirrhosis without ascites patients, 17 (18%) healthy which includes fatty liver also.

Doppler sonography is performed to determine the intrarenal arteriolar vascular resistance, defined as the resistive index (RI). The reference range for RI is 0.7 or lower. The RI can be a more sensitive parameter than the creatinine clearance. Renal duplex Doppler ultrasonography can non invasively identify a subgroup of non azotemic patients with liver disease that is at significantly higher risk

for subsequent development of kidney dysfunction and the hepatorenal syndrome. (Hepatology 1994;20:362–369.)

Out of the 49 cirrhosis with ascites patients 45 were showing elevated resistivity index, 4 were within normal range. Among 26 cirrhosis without ascites patients, 18 were showing elevated resistivity index, 8 were within normal range. Resistivity indices were increased in both cirrhosis with and without ascites. Cirrhosis with ascites=>0.87 Cirrhosis without ascites=>0.76 Fatty liver and healthy=>0.64.**In the study by Eur J Med Res. 2008 Aug 18;13(8):383-7**, **RI was significantly higher in ascitic patients compared to non-ascitic patients (0.74 vs. 0.67, p<0.01) and in non-ascitic patients with liver cirrhosis than in control subjects (0.67 vs. 0.62, p<0.01).**

In our study RI was significantly higher in ascitic patients compared to non-ascitic patients (0.87 vs. 0.76, p<0.01) and in non-ascitic patients with liver cirrhosis than in control subjects (0.76 vs. 0.64, p<0.001) .

Renal vascular resistance indices evaluated by duplex Doppler ultrasonography are already increased in the early phase of the disease. Development of ascites is associated with a further increase in the

resistance indices. Renal vasoconstriction evaluated by these indices is correlated with Child score which quantitatively measures the hepatic function in cirrhosis.

PI is also increased in cirrhosis with ascites patients compared to cirrhotics without ascites(1.12 vs1.02), cirrhotics without ascites compared to healthy (1.02vs0.08). 26% of cirrhosis with ascites patients later tends to develop HRS.

55% cirrhosis with elevated RI and normal renal function develops subsequent kidney dysfunction that is 35 patients out of 92 patients.

We conclude that patients with cirrhosis are at risk of renal deterioration, which can not be detected by serum urea, creatinine, and glomerular filtration rate. The increase of RI is associated with the progress of hepatocellular disease, and also the development of ascites and portal hypertension. Hence, monitoring RI is a non-invasive means of studying early renal hemodynamic alteration in cirrhosis.

CONCLUSION

CONCLUSION

1. We conclude that in cirrhotic, renal vascular resistance indices evaluated by duplex Doppler ultrasonography are already increased in the early phase of the disease.

2. Development of ascites is associated with a further increase in the resistance indices.

3. Renal vasoconstriction evaluated by these indices is correlated with Child score which quantitatively measures the hepatic function in cirrhosis

4. Intrarenal RI measurement is a predictor of renal vasoconstriction and serves to detect early renal function impairment in cirrhotic patients.

5. The diagnosis of elevated RI may be taken into account in the clinical management of these patients.

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BIBLIOGRAPHY

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ANNEXURE

- PROFORMA
- MASTER CHART
- ETHICAL COMMITTEE APPROVAL ORDER

PROFORMA

Name: **Age/Sex**: **IP No**:

Address: **Presenting complaints**:

Abdominal distension : Yes/ No **Duration**: days/ months

Onset : Rapid/ Insidious, Progressive/ Non-progressive

Leg swelling :Yes/ No **Duration**: days/ months

Decreased urine output :Yes/ No **Duration**: days/ months

Anuria : Yes/ No

Jaundice : Yes/ No **Duration**: days/ months

Progressive/ Non-progressive

Encephalopathy : Grade I / II / III / IV

Bleeding Tendency : Yes/ No

UGI bleed : Recent/ Remote **Duration**: days/ months

Amount **Giddiness**: Yes/ No

Malena : Yes/ No **Color**: Black/ Maroon

Other symptoms :

Past History :

UGI Bleed : Yes/ No **Duration**: **No. of episodes**

Jaundice : Yes/ No

Abdominal Surgeries : Yes/ No **Blood transfusions**: Yes/ No

Tattoo : Yes/ No **Sexual contact** : Yes/ No

Personal History:

Alcohol intake : Duration: Years Amount: ml/day

Frequency: Daily/ Weekly – / Occasional

Smoking : Yes/ No Duration:

Vaccination status : Complete/ Incomplete/ No

Examination :

Jaundice: Yes/ No Pallor: Yes/ No

Signs of CLD: Spider nevi/ parotid enlargement/ gynecomastia/ testicular atrophy/ sparse axillary hair / Dupuytren contracture

Avitaminosis: Yes/ No

Abdomen:

Hepatomegaly: Yes/ No **Size**: **Surface**: **Borders**: Span:

Splenomegaly: Yes/ No **Size**:

Free fluid : Minimal/ Moderate/ Tense **Tenderness**: Present/ Absent

Investigations:

TC: DC: N/L/E:

Platelet count: ESR:

Blood urea						
Sr. Creatinine						
Blood sugar						
Sr. Sodium						
LFT						
AST						
ALT						
SAP						
STB						
Direct						
STP						
ALBUMIN						

USG abdomen:

Liver:

PV:

Spleen:

Kidneys

Portal Doppler:

Liver:

PV:

Spleen:

Resistive Index:

Peak systolic velocities:

Peak diastolic velocities:

Mean flow velocities:

Pulsatile index:

Resistive index:

Peak systolic velocity/peak diastolic velocity ratio

Outcome: Follow-up:

SL NO	AGE	SEX	CAUSE	ASC ITES	U.O	S.Na	LFT	UREA	CREAT ININE	USG ABD	PORTAL DOPPLER	R.I	P.I
1	57	M	ALC CIRR	Y	Nl	138	RSD	NL	NL	DCLD ASC	PHT	0.76	1.12
2	51	M	ALC CIRR	Y	Nl	134	RSD	NL	NL	DCLD ASC	PHT	0.76	1.07
3	53	M	ALC CIRR	Y	Nl	132	RSD	NL	NL	DCLD ASC	PHT	0.81	1.38
4	33	M	HBS CIRR	N	Nl	136	RSD	NL	NL	CLD	CLD	0.63	1.00
5	46	M	ALC CIRR	Y	Nl	131	RSD	NL	NL	DCLD ASC	PHT	0.77	1.21
6	52	M	ALC CIRR	N	Nl	137	RSD	NL	NL	CLD	CLD	0.77	1.07
7	43	M	ALC CIRR	Y	Nl	140	RSD	NL	NL	DCLD ASC	PHT	0.82	1.42
8	49	M	ALC CIRR	N	Nl	137	RSD	NL	NL	CLD	CLD	0.75	1.01
9	50	M	ALC CIRR	Y	Nl	130	RSD	NL	NL	DCLD ASC	PHT	0.64	1.24
10	54	M	ALC CIRR	N	Nl	132	RSD	NL	NL	CLD	CLD	0.71	1.06
11	43	F	ALC CIRR	N	Nl	133	RSD	NL	NL	CLD	CLD	0.77	1.12
12	46	M	HBS CIRR	Y	Nl	134	RSD	NL	NL	DCLD ASC	PHT	0.81	1.38
13	48	M	ALC CIRR	N	Nl	137	RSD	NL	NL	CLD	CLD	0.61	0.09
14	59	M	CRYPT CIRR	Y	Nl	140	RSD	NL	NL	DCLD ASC	PHT	0.82	1.39
15	52	M	ALC CIRR	N	Nl	136	RSD	NL	NL	CLD	CLD	0.76	1.06
16	56	M	ALC CIRR	N	Nl	133	RSD	NL	NL	CLD	CLD	0.76	1.05
17	47	M	ALC CIRR	Y	Nl	134	RSD	NL	NL	DCLD ASC	PHT	0.78	1.46
18	44	M	ALC CIRR	Y	Nl	137	RSD	NL	NL	DCLD ASC	PHT	0.77	1.38
19	50	F	ALC CIRR	N	Nl	134	RSD	NL	NL	CLD	CLD	0.78	1.06
20	56	M	HBS CIRR	N	Nl	132	RSD	NL	NL	CLD	CLD	0.64	1.03
21	51	M	HBS CIRR	N	Nl	138	RSD	NL	NL	CLD	CLD	0.78	1.06
22	42	M	ALC CIRR	Y	Nl	139	RSD	NL	NL	DCLD ASC	PHT	0.76	1.43
23	46	M	ALC CIRR	Y	Nl	138	RSD	NL	NL	DCLD ASC	PHT	0.79	1.40

24	49	M	ALC CIRR	N	Nl	134	RSD	NL	NL	CLD	CLD	0.79	1.07
25	54	F	ALC CIRR	Y	Nl	132	RSD	NL	NL	DCLD ASC	PHT	0.60	1.28
26	58	M	ALC CIRR	Y	Nl	136	RSD	NL	NL	DCLD ASC	PHT	0.82	1.34
27	43	M	CRYP CIRR	N	Nl	134	RSD	NL	NL	CLD	CLD	0.74	1.03
28	59	M	ALC CIRR	Y	Nl	137	RSD	NL	NL	DCLD ASC	PHT	0.78	1.26
29	40	F	HBS CIRR	N	Nl	138	RSD	NL	NL	CLD	CLD	0.62	1.03
30	41	M	CRYP CIRR	N	Nl	134	RSD	NL	NL	CLD	CLD	0.61	1.01
31	47	M	AIC CIRR	Y	Nl	133	RSD	NL	NL	DCLD ASC	PHT	0.78	1.42
32	56	M	HBS CIRR	Y	Nl	143	RSD	NL	NL	DCLD ASC	PHT	0.78	1.39
33	54	M	HBS CIRR	N	Nl	142	RSD	NL	NL	CLD	CLD	0.73	1.02
35	55	M	ALC CIRR	N	Nl	132	RSD	NL	NL	CLD	CLD	0.72	1.01
36	34	F	CRYP CIRR	Y	Nl	136	RSD	NL	NL	DCLD ASC	PHT	0.78	1.38
37	60	M	ALC CIRR	Y	Nl	139	RSD	NL	NL	DCLD ASC	PHT	0.76	1.43
38	45	M	ALC CIRR	Y	Nl	140	RSD	NL	NL	DCLD ASC	PHT	0.78	1.47
39	55	M	HBS CIRR	N	Nl	134	RSD	NL	NL	CLD	CLD	0.61	1
40	58	F	ALC CIRR	N	Nl	133	RSD	NL	NL	CLD	CLD	0.79	1.06
41	47	M	ALC CIRR	Y	Nl	135	RSD	NL	NL	DCLD ASC	PHT	0.78	1.46
42	40	M	HBS CIRR	Y	Nl	136	RSD	NL	NL	DCLD ASC	PHT	0.62	1.42
43	49	M	ALC FAT. LIV	N	Nl	141	NL	NL	NL	CLD	CLD	0.62	0.83
44	58	F	ALC CIRR	Y	Nl	138	RSD	NL	NL	DCLD ASC	PHT	0.82	1.46
45	53	M	ALC FAT. LIV	N	Nl	132	NL	NL	NL	CLD	NL	0.63	0.86
46	47	M	ALC CIRR	Y	Nl	131	RSD	NL	NL	DCLD ASC	PHT	0.76	1.12
47	50	M	ALC CIRR	N	Nl	142	RSD	NL	NL	CLD	CLD	0.71	1.07
48	43	M	CRYP CIRR	N	Nl	134	RSD	NL	NL	CLD	CLD	0.72	1.00
49	40	M	ALC CIRR	Y	Nl	132	RSD	NL	NL	DCLD ASC	PHT	0.81	1.21

50	52	M	ALC FAT LIV	N	Nl	141	NL	NL	NL	NL	NL	0.64	0.82
51	58	F	HBS CIRR	Y	Nl	136	RSD	NL	NL	DCLD ASC	PHT	0.80	1.13
52	45	M	HBS CIRR	Y	Nl	137	RSD	NL	NL	DCLD ASC	PHT	0.83	1.35
53	61	M	ALC CIRR	N	Nl	134	RSD	NL	NL	CLD	CLD	0.71	0.91
54	47	M	ALC CIRR	Y	Nl	138	RSD	NL	NL	DCLD ASC	PHT	0.80	1.39
55	46	M	ALC CIRR	Y	Nl	133	RSD	NL	NL	DCLD ASC	PHT	0.84	1.37
56	58	F	ALC CIRR	Y	Nl	132	RSD	NL	NL	DCLD ASC	PHT	0.83	1.43
57	57	M	ALC CIRR	Y	Nl	136	RSD	NL	NL	DCLD ASC	PHT	0.77	1.40
58	51	M	HBS CIRR	Y	Nl	144	RSD	NL	NL	DCLD ASC	PHT	0.79	1.38
59	53	M	ALC CIRR	Y	Nl	137	RSD	NL	NL	DCLD ASC	PHT	0.79	1.28
60	56	M	ALC CIRR	Y	Nl	135	RSD	NL	NL	DCLD ASC	PHT	0.77	1.23
61	52	F	HBS CIRR	Y	Nl	140	RSD	NL	NL	DCLD ASC	PHT	0.82	1.32
62	47	M	ALC CIRR	Y	Nl	130	RSD	NL	NL	DCLD ASC	PHT	0.80	1.65
63	57	M	ALC CIRR	Y	Nl	132	RSD	NL	NL	DCLD ASC	PHT	0.81	1.46
64	49	M	CRYP CIRR	Y	Nl	135	RSD	NL	NL	DCLD ASC	PHT	0.77	1.44
65	44	M	HBS CIRR	Y	Nl	141	RSD	NL	NL	DCLD ASC	PHT	0.64	1.43
66	58	M	ALC FAT LIV	N	Nl	139	NL	NL	NL	NL	NL	0.62	0.91
67	56	F	HBS CIRR	Y	Nl	134	RSD	NL	NL	DCLD ASC	PHT	0.81	1.12
68	43	M	ALC CIRR	Y	Nl	138	RSD	NL	NL	DCLD ASC	PHT	0.79	1.45
69	41	M	CRYP CIRR	N	Nl	135	RSD	NL	NL	CLD	CLD	0.77	1.01
70	57	M	ALC FAT. LIV	N	Nl	138	NL	NL	NL	CLD	CLD	0.64	0.82
71	60	F	ALC CIRR	Y	Nl	140	RSD	NL	NL	DCLD ASC	PHT	0.79	1.37
72	56	M	ALC CIRR	Y	Nl	130	RSD	NL	NL	DCLD ASC	PHT	0.81	1.45

73	49	M	CRYP CIRR	N	Nl	131	RSD	NL	NL	CLD	CLD	0.70	1
74	53	F	HBS CIRR	N	Nl	135	RSD	NL	NL	CLD	CLD	0.71	1.01
75	55	M	ALC CIRR	Y	Nl	139	RSD	NL	NL	DCLD ASC	PHT	0.77	1.37
76	64	M	ALC CIRR	Y	Nl	134	RSD	NL	NL	DCLD ASC	PHT	0.80	1.43
77	42	M	ALC CIRR	Y	Nl	142	RSD	NL	NL	DCLD ASC	PHT	0.87	1.42
78	55	M	ALC CIRR	Y	Nl	130	RSD	NL	NL	DCLD ASC	PHT	0.77	1.33
79	47	M	HBS CIRR	N	Nl	135	RSD	NL	NL	CLD	CLD	0.76	1.02
80	61	M	ALC CIRR	Y	Nl	137	RSD	NL	NL	DCLD ASC	PHT	0.78	1.56
81	50	M	FAT. LIV	N	NL	130	NL	NL	NL	NL	NL	0.62	1.03
82	60	M	HEALT HY	N	NL	132	NL	NL	NL	NL	NL	0.60	0.82
83	58	M	HEALT HY	N	NL	138	NL	NL	NL	NL	NL	0.58	0.81
84	47	F	FAT. LIV	N	NL	136	NL	NL	NL	NL	NL	0.59	1.00
85	49	M	HEALT HY	N	NL	140	NL	NL	NL	NL	NL	0.58	0.80
86	44	M	HEALT HY	N	NL	138	NL	NL	NL	NL	NL	0.56	0.83
87	57	M	FAT. LIV	N	NL	135	NL	NL	NL	NL	NL	0.61	1.01
88	59	M	HEALT HY	N	NL	137	NL	NL	NL	NL	NL	0.63	0.80
89	60	M	HEALT HY	N	NL	136	NL	NL	NL	NL	NL	0.64	0.82
90	42	F	FAT. LIV	N	NL	133	NL	NL	NL	NL	NL	0.66	0.89
91	53	M	HEALT HY	N	NL	143	NL	NL	NL	NL	NL	0.60	0.93
92	46	M	FAT. LIV	N	NL	140	NL	NL	NL	NL	NL	0.67	0.92

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ABBREVIATIONS

HRS-HEPATORENAL SYNDROME.

RI-RESISTIVITY INDEX.

PI-PULSATALITY INDEX.

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-600 003

Telephone 25363970
Fax 044 2535115
Dated : 12.05.2010

L.Dis.No.14597/ME5/Ethics Dean/MMC/2010

Title of the work : "Early detection of renal blood flow impedance by colour doppler in chronic liver disease with normal renal parameters."

Principal Investigator : Dr. V. Dhurgesa Nanthini
Designation : Pg in MD General Medicine
Department : Madras Medical College & GGH, Ch-3.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 12th May 2010 at 2.p.m in Pharmacology Seminar Hall, Madras Medical College, Chennai -3

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
4. You should not deviate form the area of the work for which you applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulation of the institution(s).
7. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, MMC, CHENNAI

CHAIRMAN
IEC, MMC, CHENNAI

DEAN
MADRAS MEDICAL COLLEGE,
CHENNAI -3